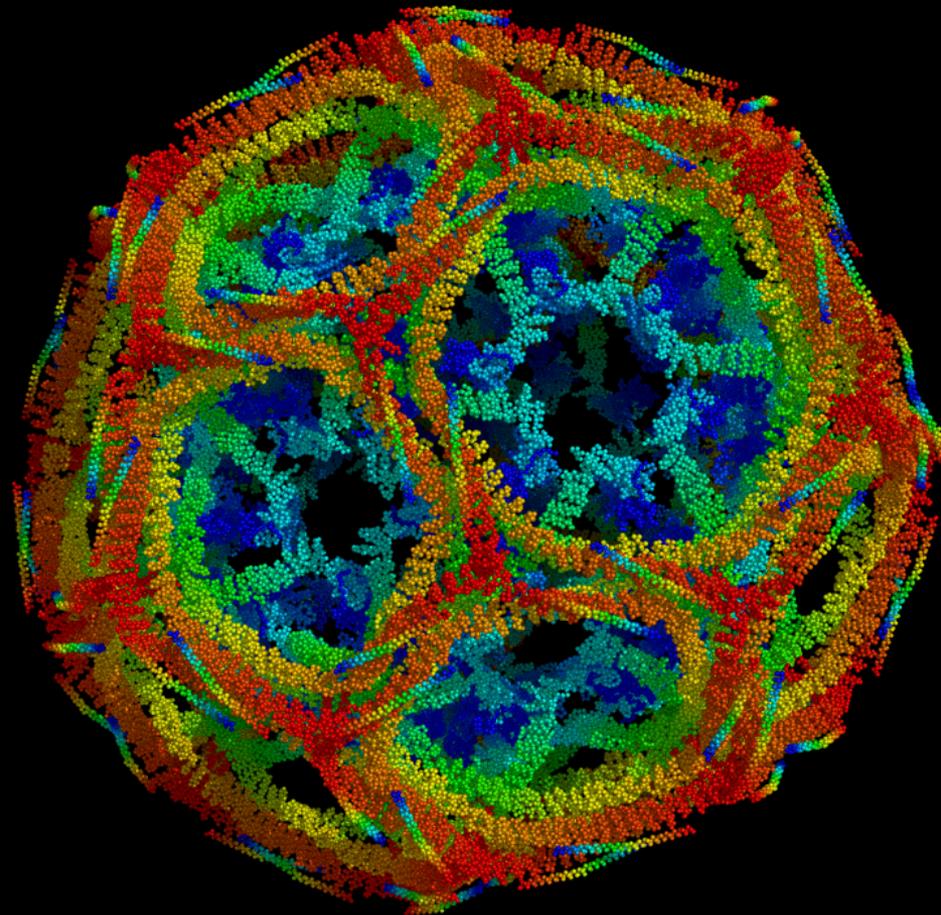


# *Genetic Disorders of Protein Coats*

*Juan S. Bonifacino*

*Cell Biology and Metabolism Program, NICHD, NIH*



# *Genetic Disorders of Protein Coats*

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- **Protein coats involved in intracellular transport**
- **Diseases caused by mutations in coat proteins**
- **AP-3 defects in Hermansky-Pudlak syndrome**
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# *Vesicular Transport Earns a Nobel*



*James Rothman*

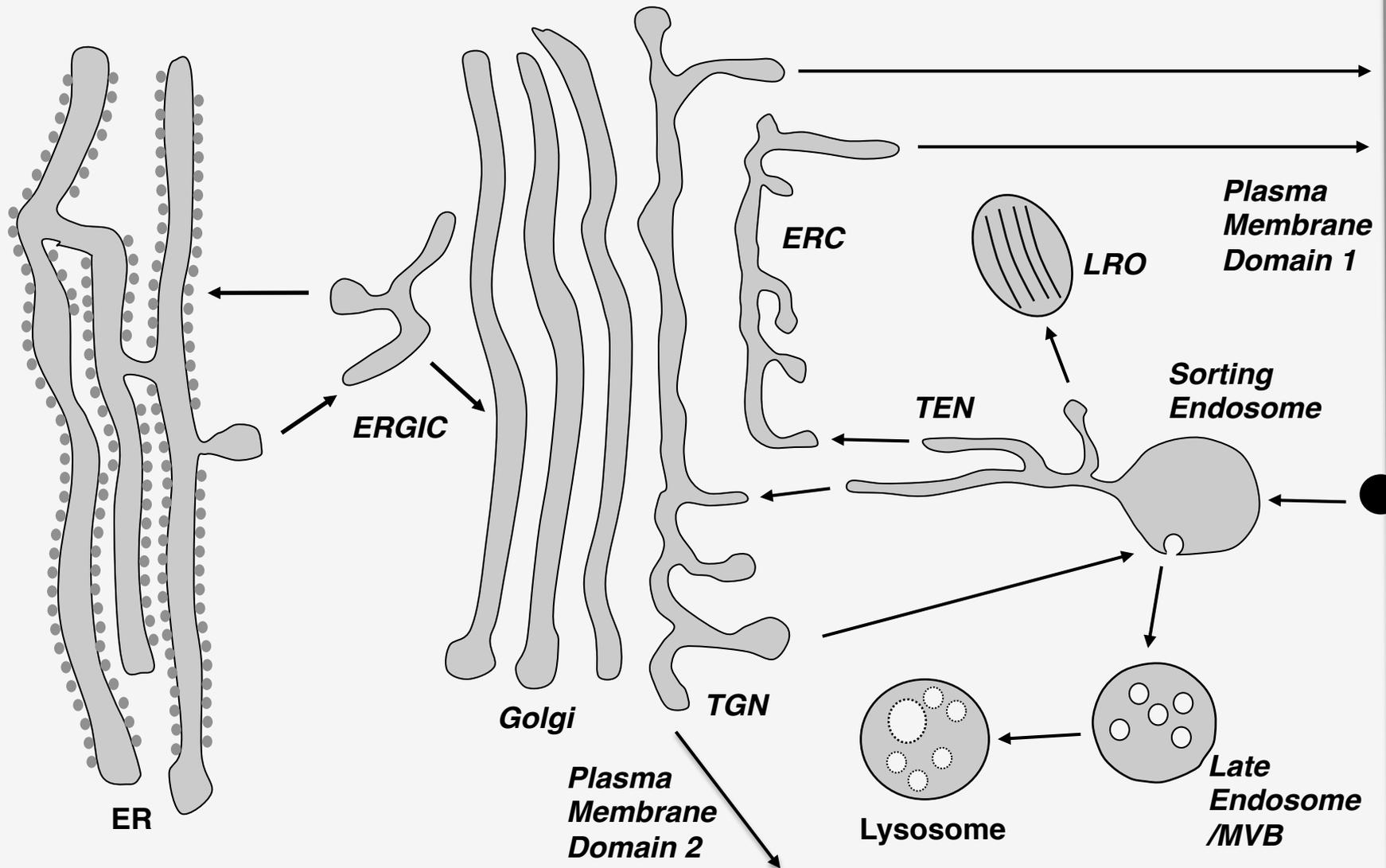
*Randy Schekman*

*Thomas Südhof*

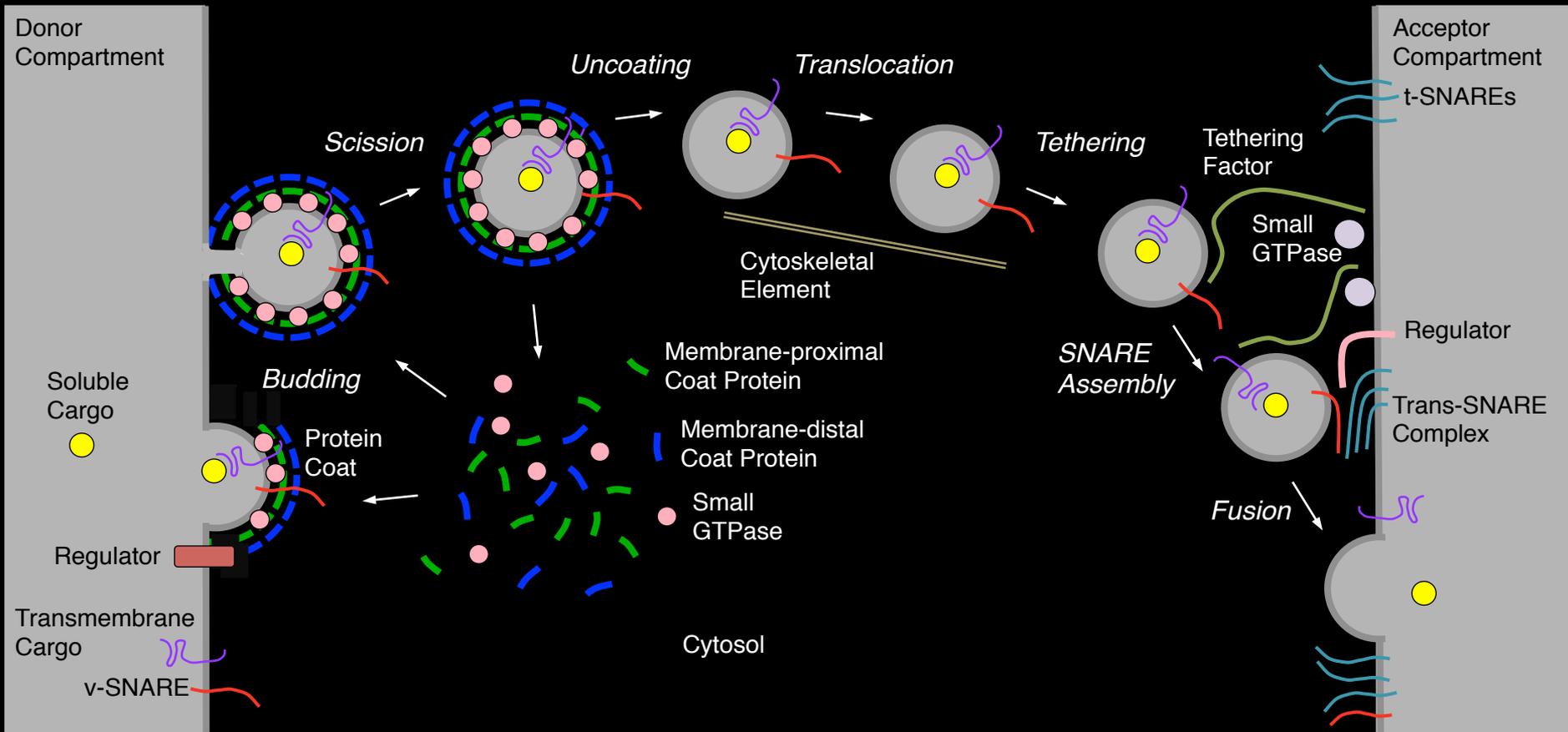
**2013 Nobel Prize for Medicine or Physiology**



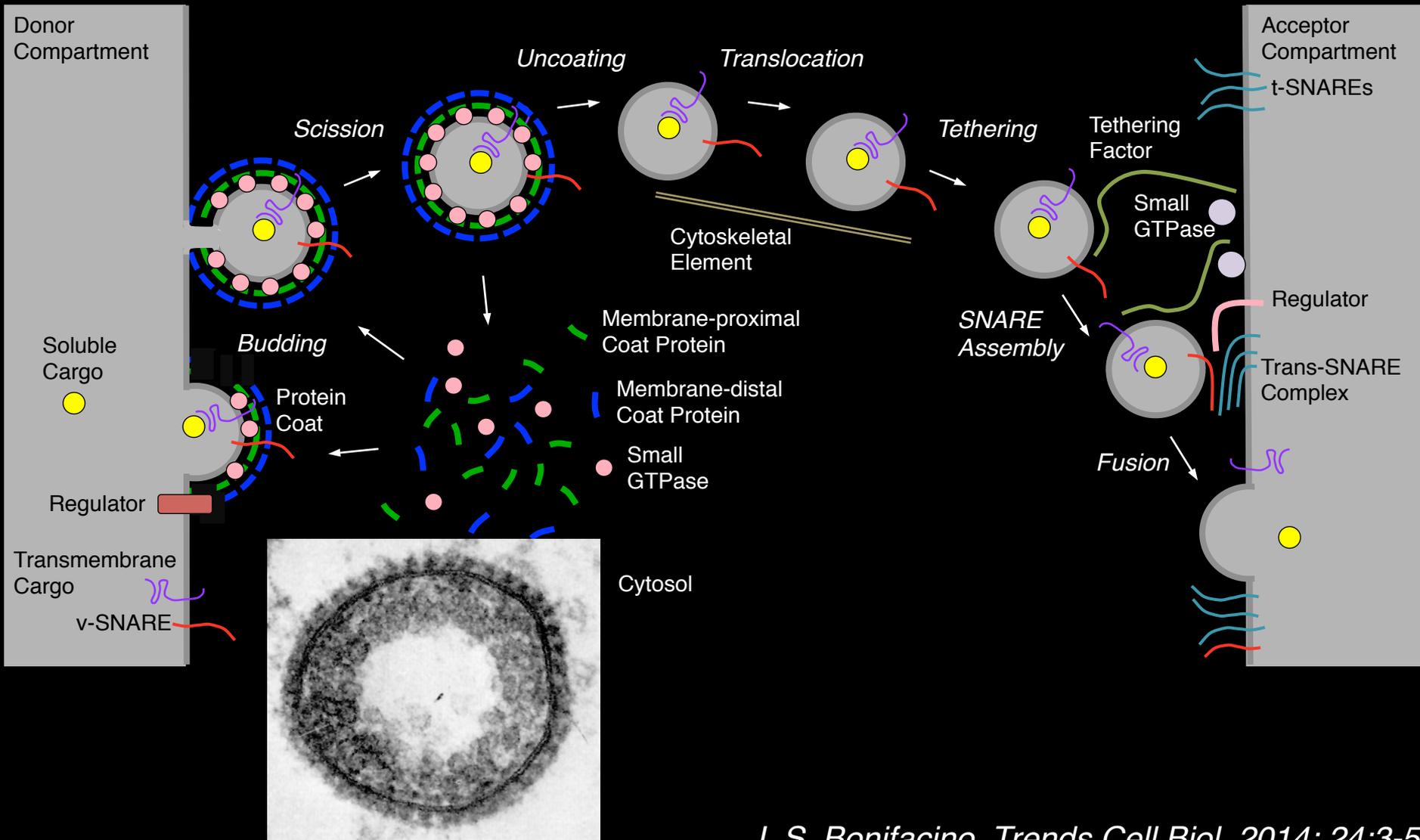
# The Endomembrane System



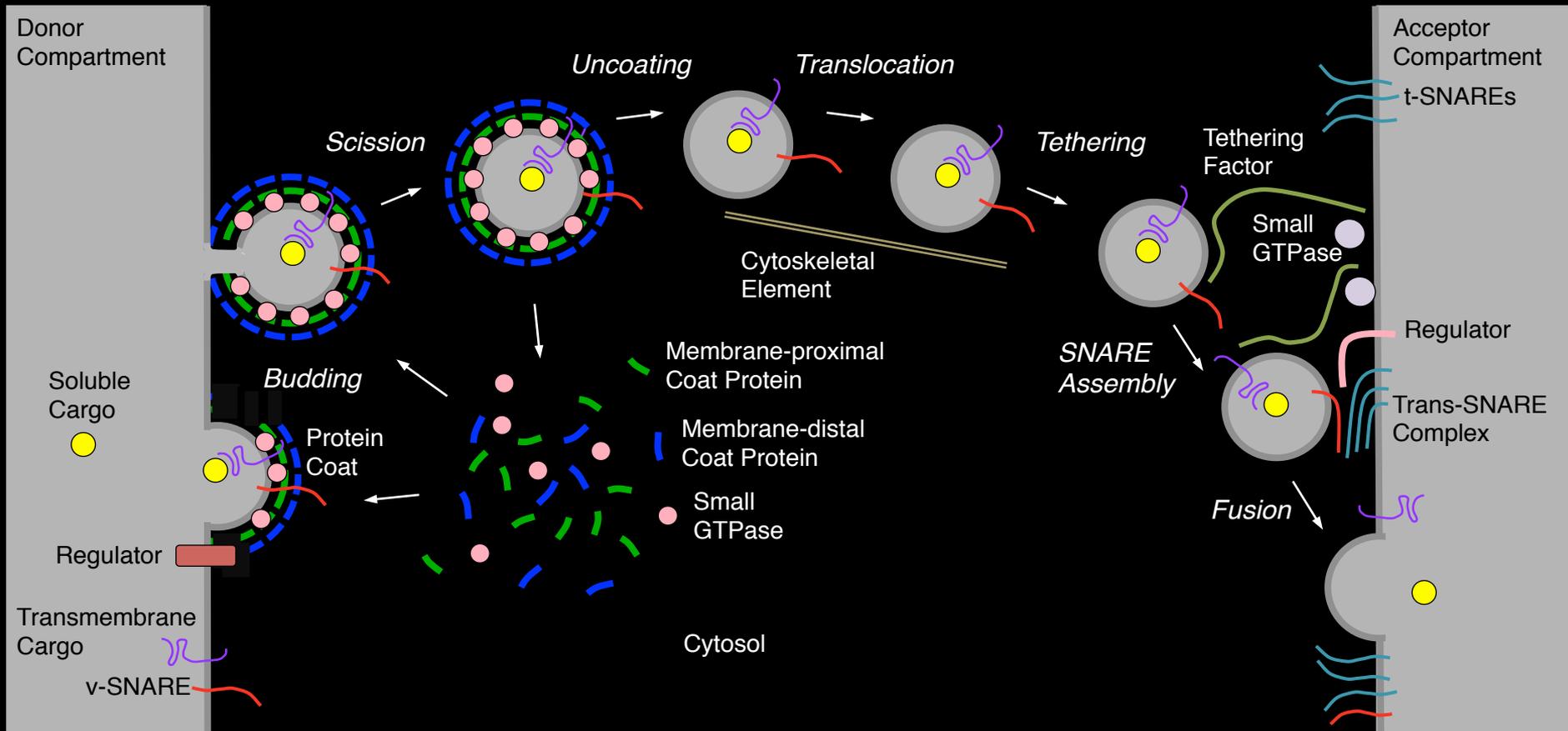
# The Life Cycle of a Transport Vesicle



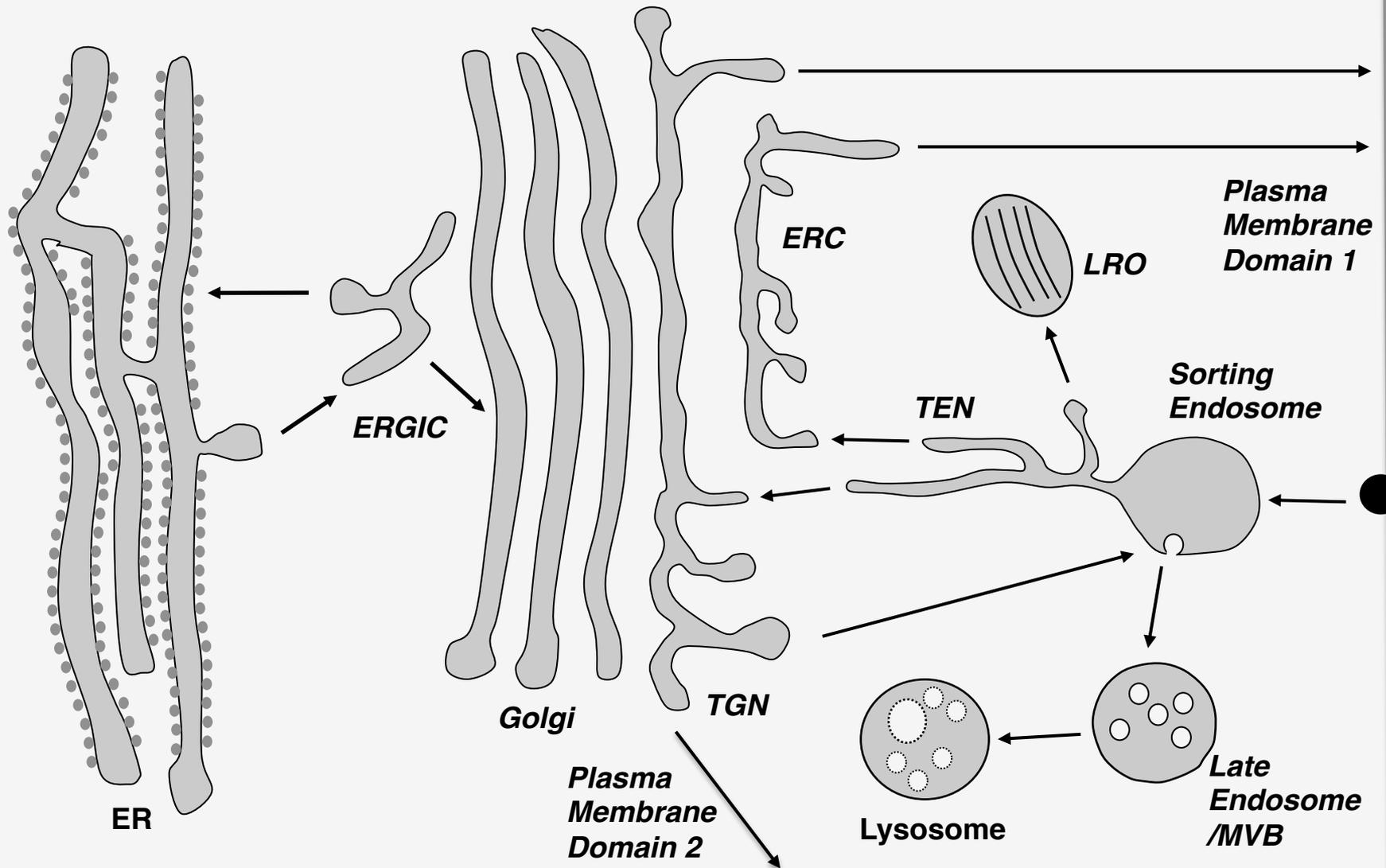
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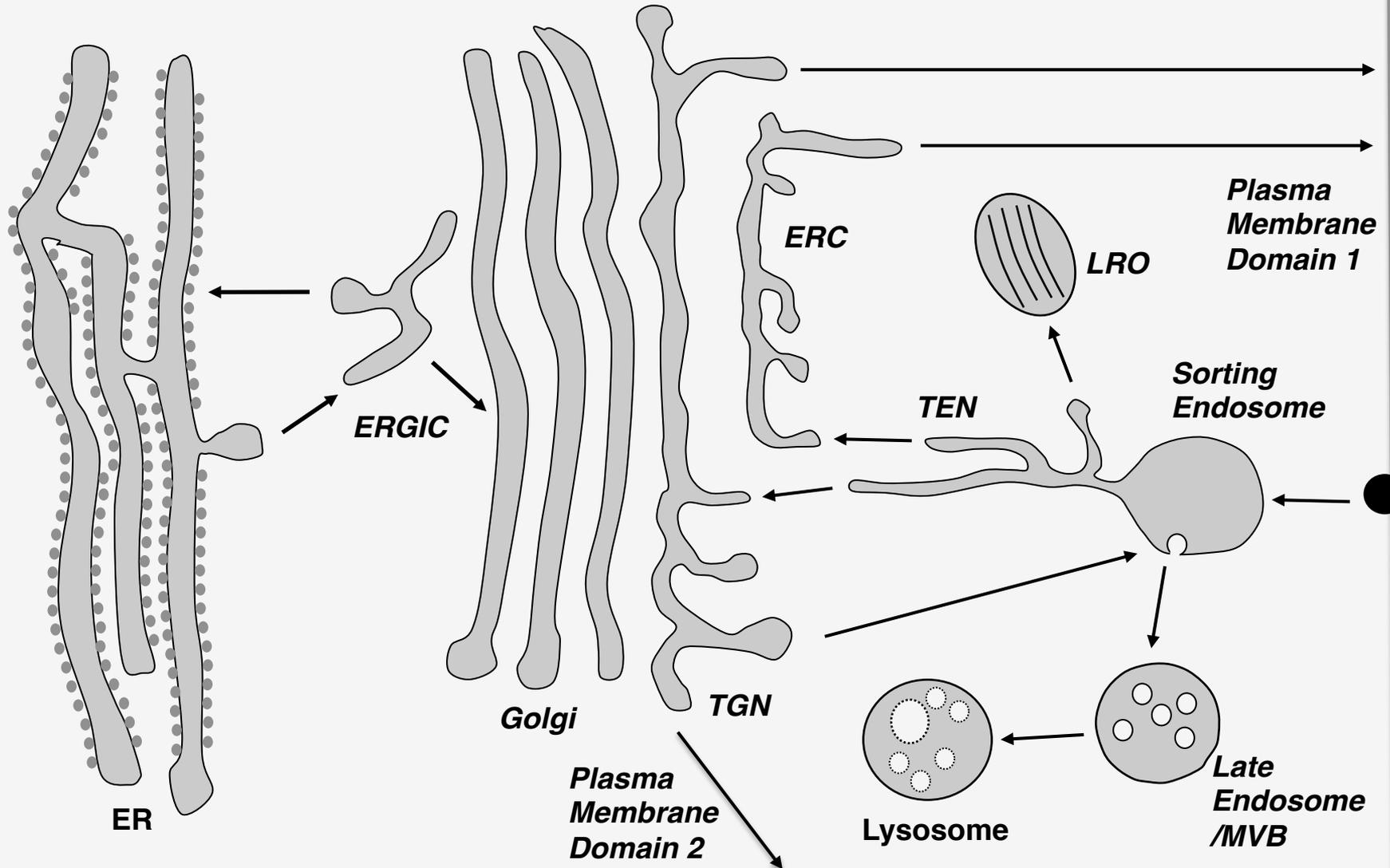
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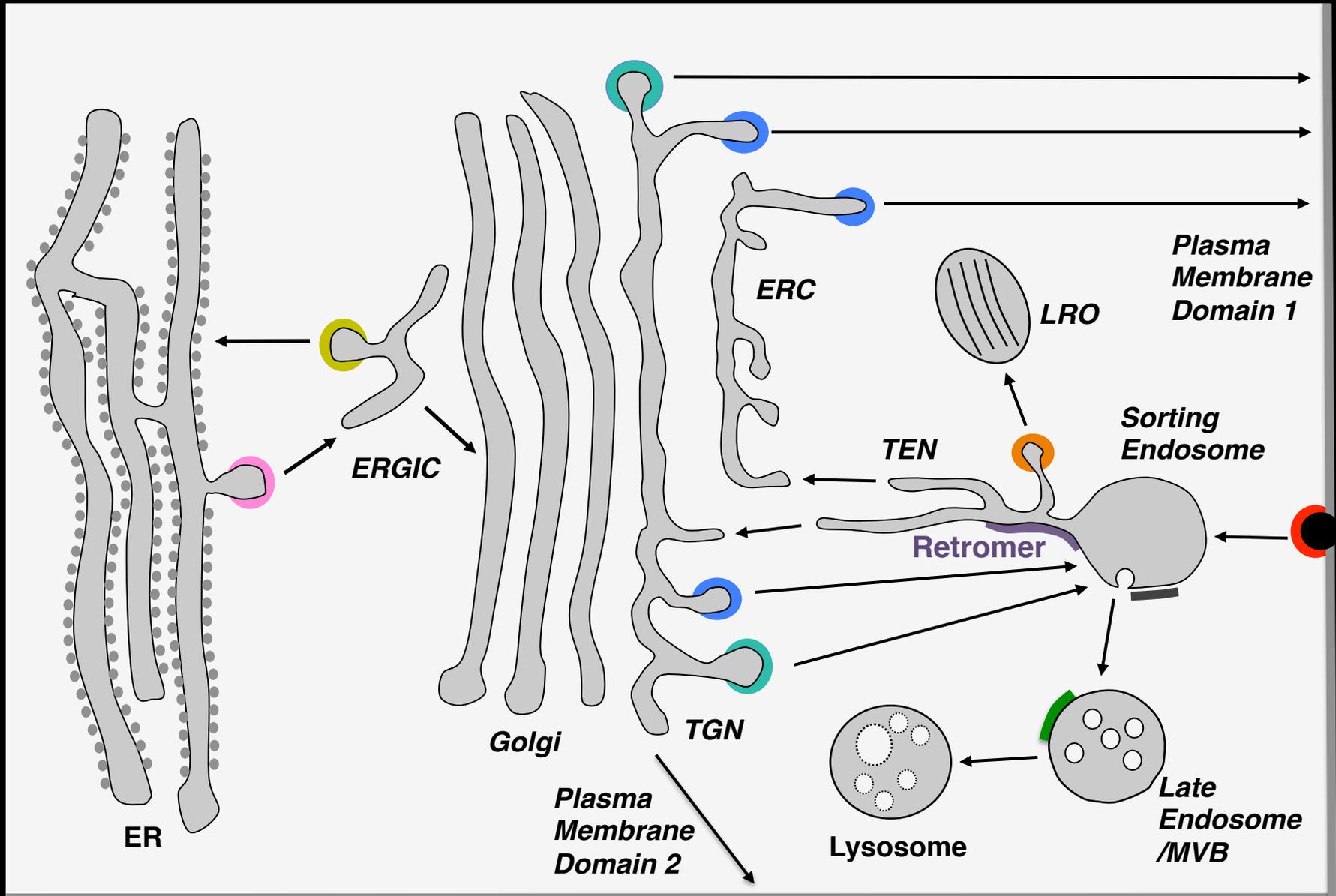
# The Endomembrane System



# Protein Coats in the Endomembrane System

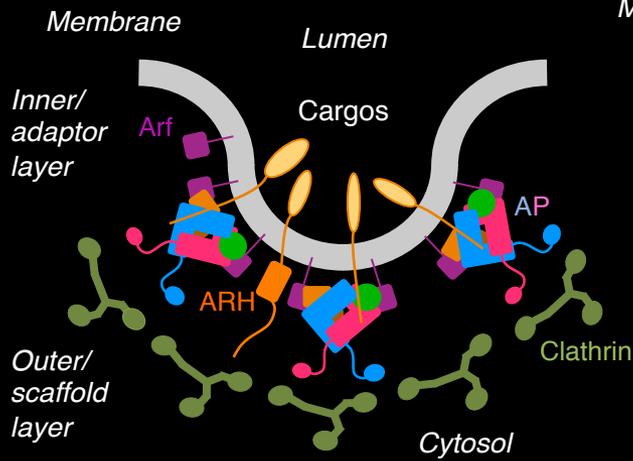


# Protein Coats in the Endomembrane System

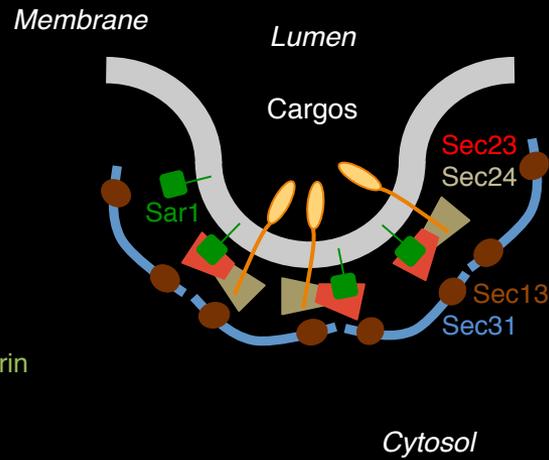


# Types of Protein Coat

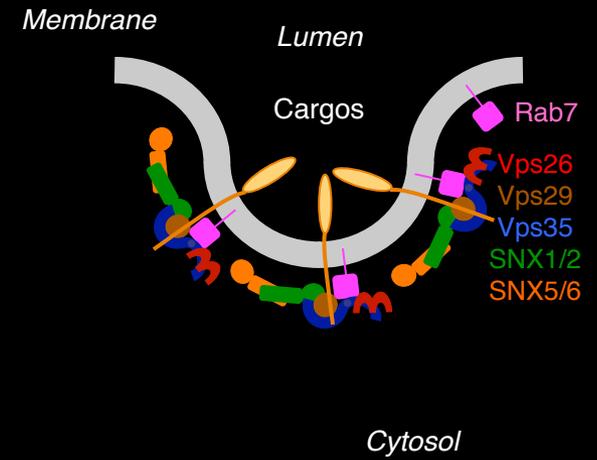
Clathrin/AP-like



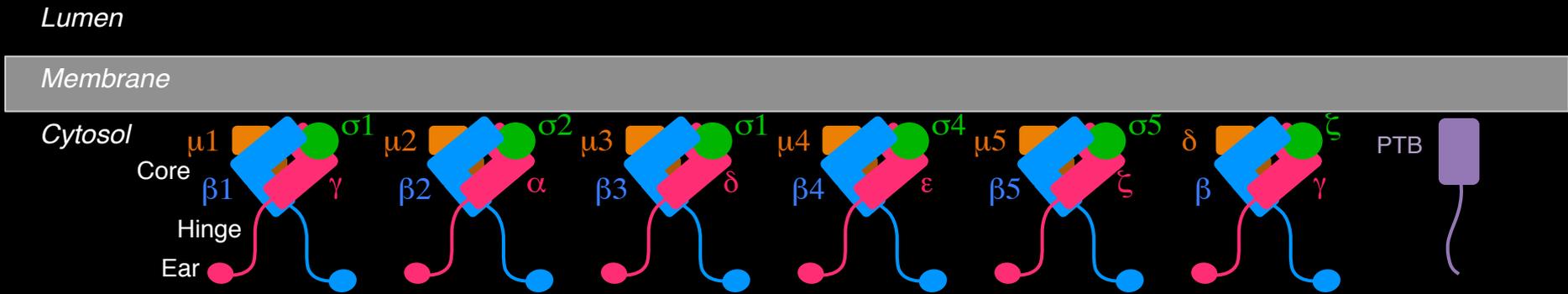
COPII



Retromer

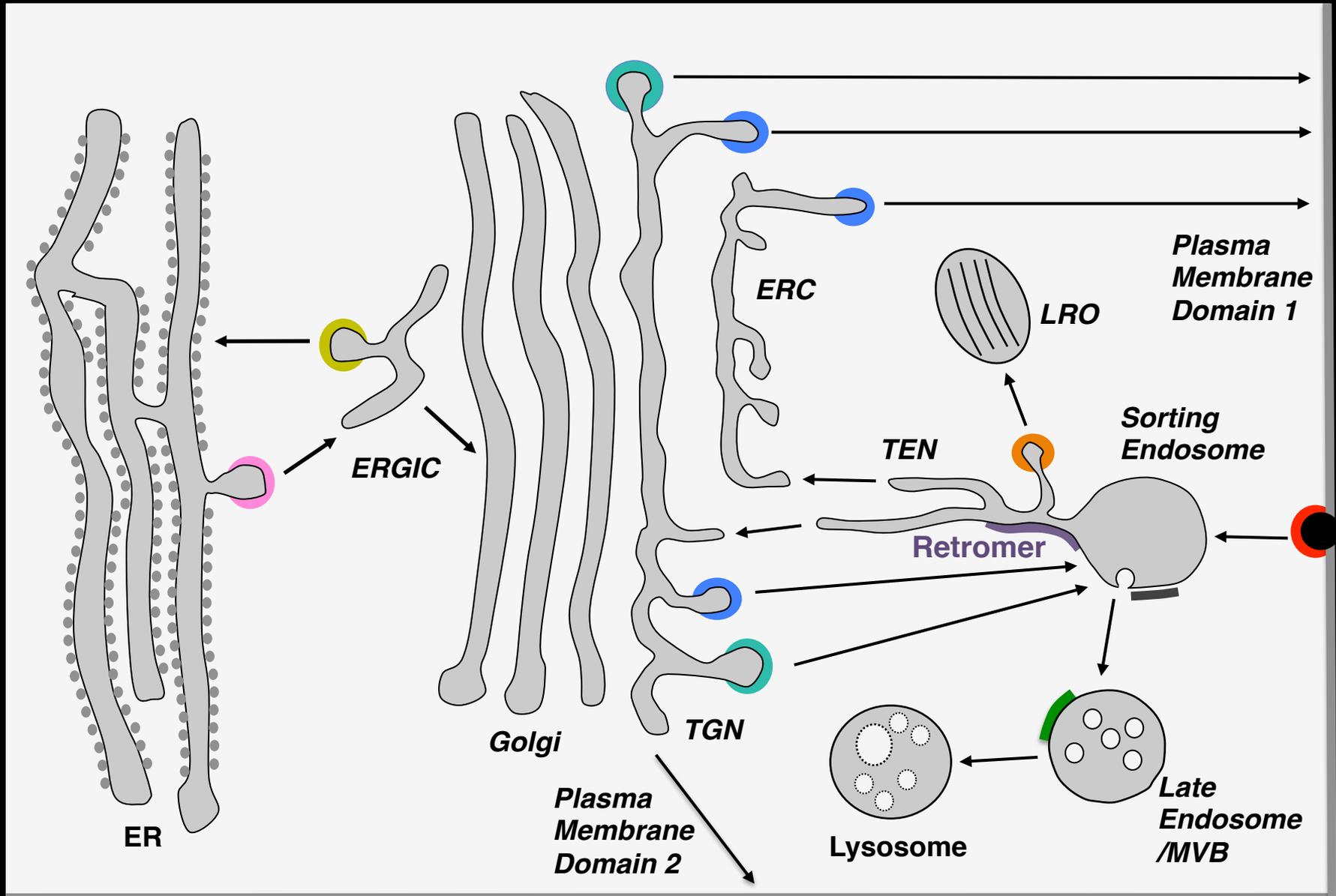


# AP-type Coats

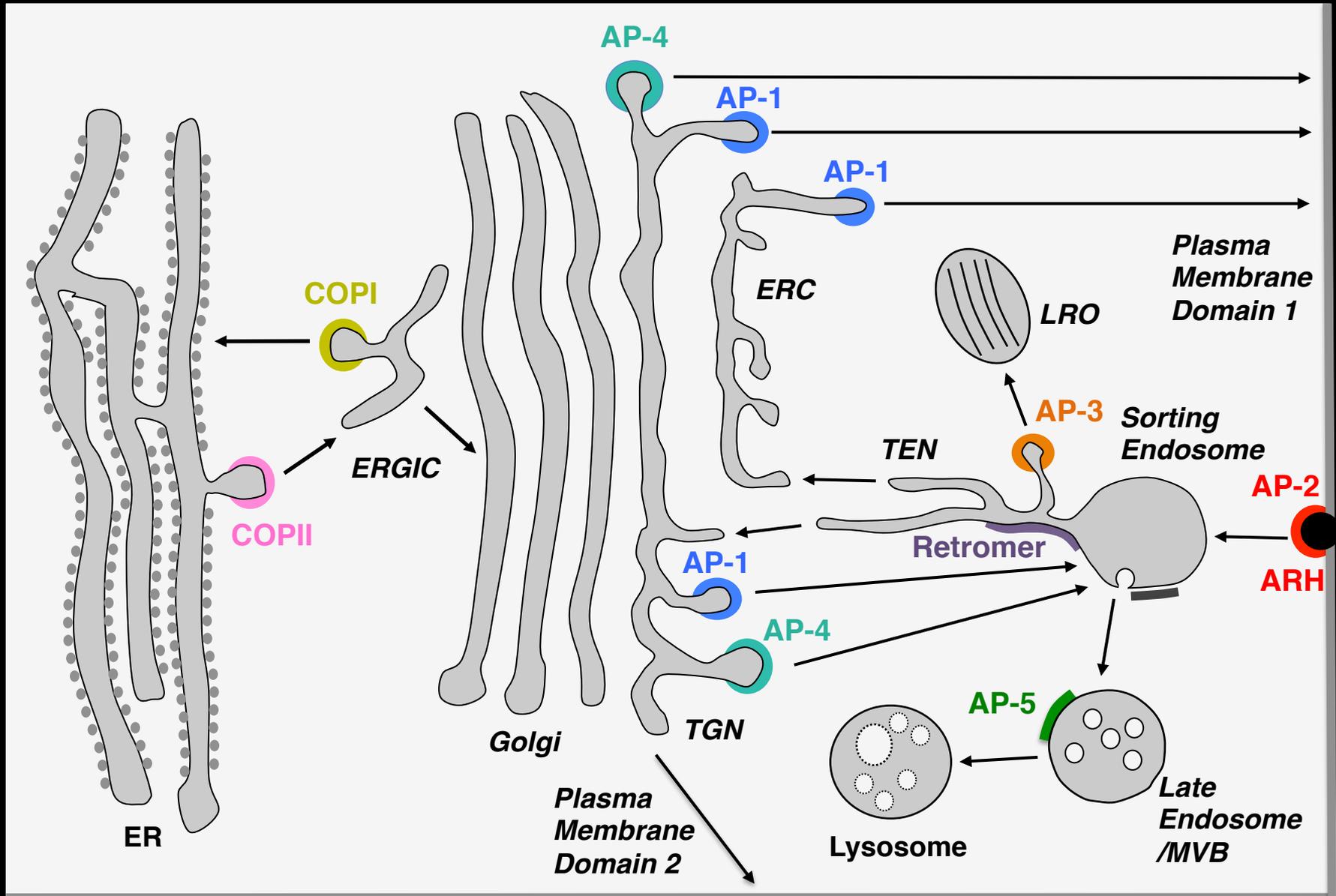


Adaptors	AP-1	AP-2	AP-3	AP-4	AP-5	COPI	ARH
Scaffolds	Clathrin	Clathrin	Clathrin? Vps41?	Unknown	SPG11-SPG15	$\alpha$ - $\beta'$ - $\epsilon$ -COP	Clathrin
Docking factors	Arf, PtdIns4P	PtdIns(4,5)P	Arf, PtdIns3P	Arf	PtdIns3P	Arf	PtdIns(4,5)P
Sorting signals	YXX $\emptyset$ [DE]XXXL[LI] Non-canonical	YXX $\emptyset$ [DE]XXXL[LI]	YXX $\emptyset$ [DE]XXXL[LI]	YX[FYL][FL]E Non-canonical	?	KKXX KXKXX (bind to scaffold)	[FY]XNPX[YF]
Localization	TGN/Endos.	PM	TEN	TGN	Late Endos.	ERGIC/Golgi	PM/Endos.
Functions	TGN $\leftrightarrow$ Endos. Polarized sorting Others	Endocytosis	LRO sorting	TGN $\rightarrow$ Endos. Polarized sorting	?	Golgi $\rightarrow$ ER	LDL R endocytosis

# Protein Coats in the Endomembrane System



# Protein Coats in the Endomembrane System

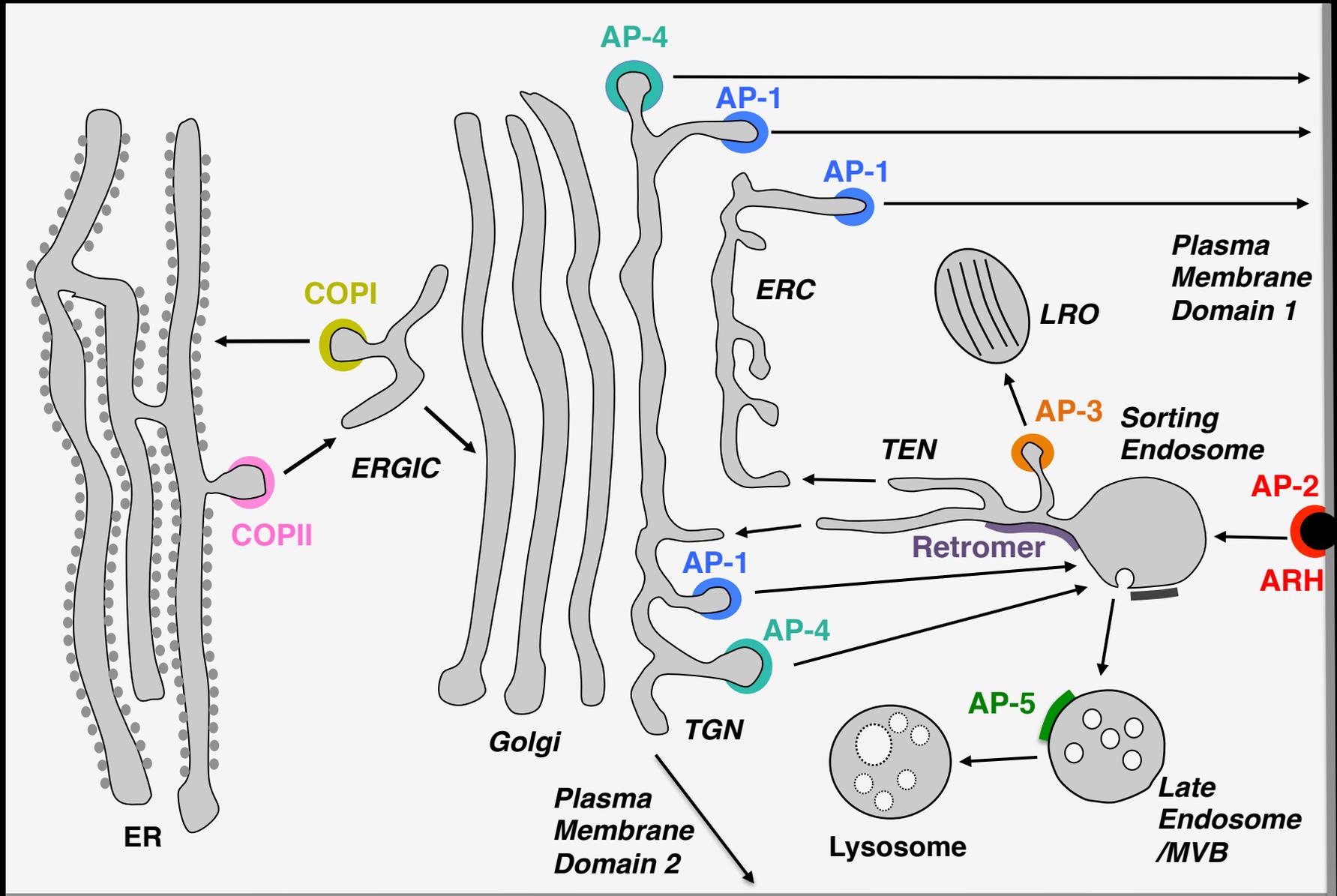


# *Genetic Disorders of Protein Coats*

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- **Diseases caused by mutations in coat proteins**
- AP-3 defects in Hermansky-Pudlak syndrome
- AP-1 defects in neurodevelopmental disorders

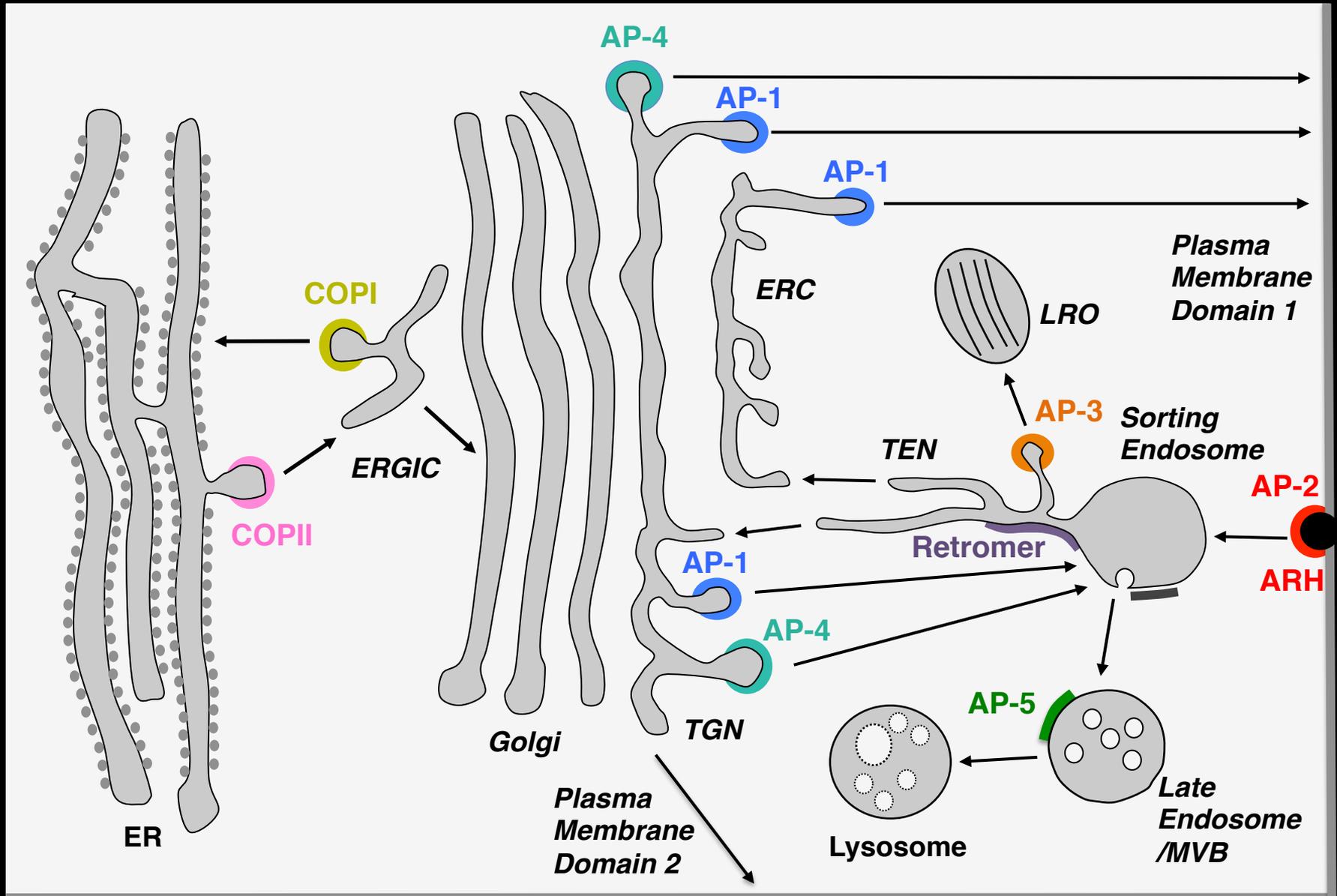
# Protein Coats in the Endomembrane System



# ***COPII Diseases***

Subunit	Gene	OMIM #	Disease
Sec23A	<i>SEC23A</i> (14q21.1)	610511/ 607812	Boyadjiev-Jabs syndrome or craniolenticulosutural dysplasia, autosomal recessive
Sec23B	<i>SEC23B</i> (20p11.23)	610512/ 224100	Congenital dyserythropoietic anemia type II (CDAN2), autosomal recessive
Sar1B	<i>SAR1B</i> (5q31.1)	607690/ 246700	Anderson disease or chylomicron retention disease, autosomal recessive

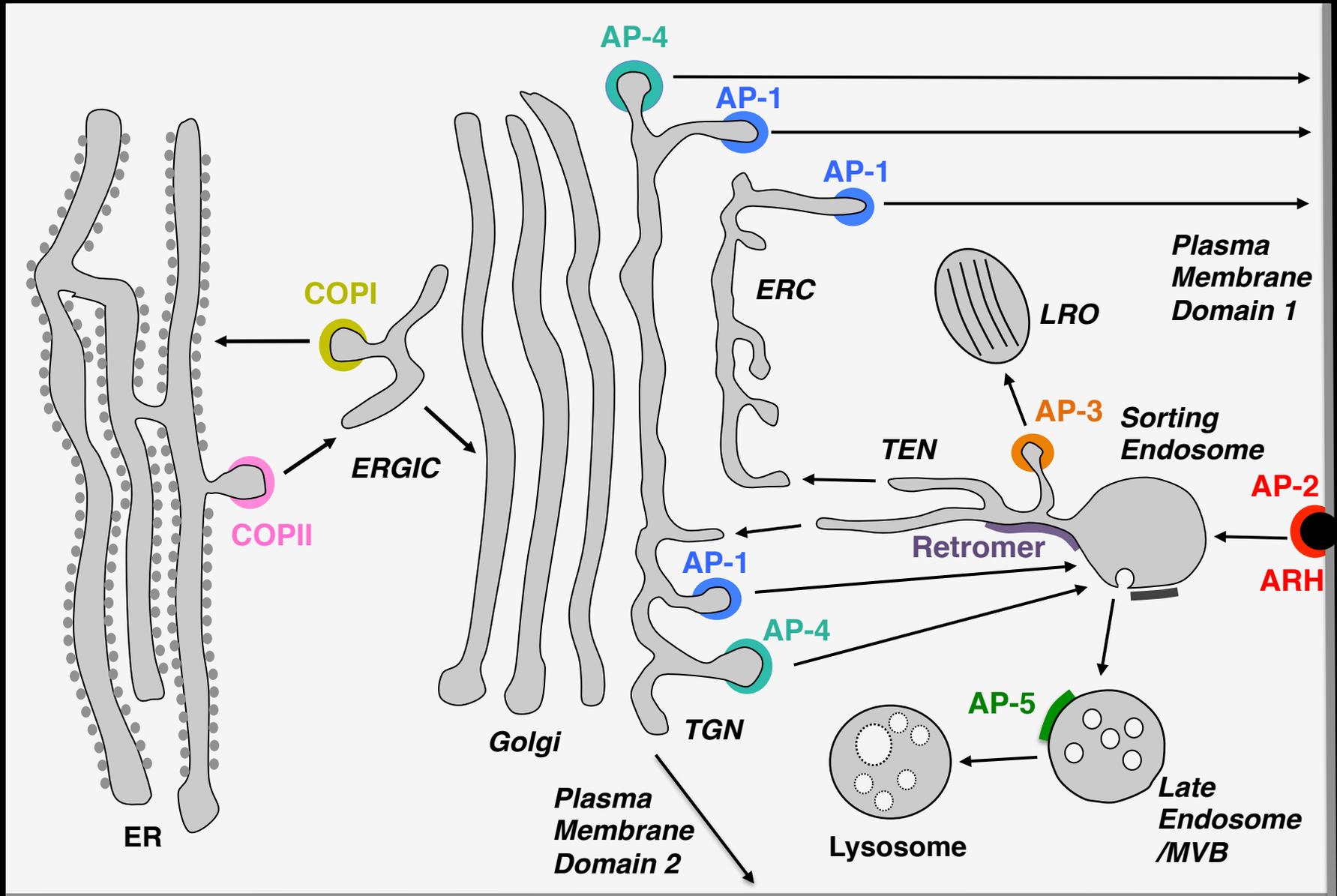
# Protein Coats in the Endomembrane System



# AP-1 Diseases

Subunit	Gene	OMIM #	Disease
$\sigma$ 1A	<i>AP1S1</i> (7q22.1)	603531/ 609313	MEDNIK (Mental retardation, Enteropathy, Deafness, peripheral Neuropathy, Ichthyosis, Keratoderma) syndrome, or EKV3 (Erythrokeratoderma Variabilis type 3)
$\sigma$ 1B	<i>AP1S2</i> (Xp22.2)	300629/ 300630/ 304340	Fried syndrome: X-linked mental retardation (MRXSF)  Also Pettigrew syndrome: X-linked Dandy-Walker malformation with intellectual disability, basal ganglia disease and seizures

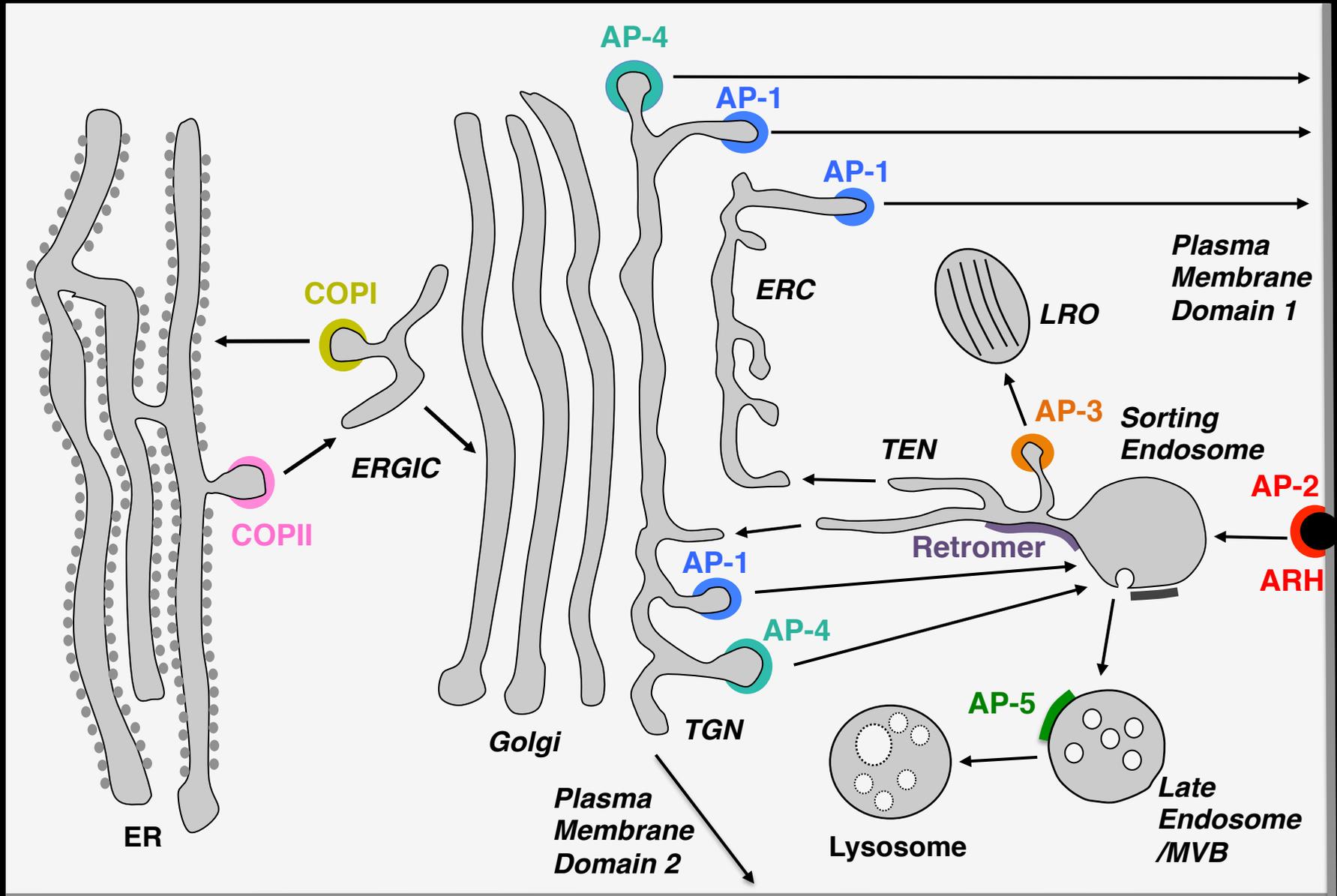
# Protein Coats in the Endomembrane System



# *Diseases of AP-2 and the Endocytic Machinery*

Subunit	Gene	OMIM #	Disease
$\sigma 2$	<i>AP2S1</i> (19q13.32)	602242/ 600740	Hypocalciuric hypercalcemia, familial, type III, autosomal dominant
ARH	<i>LDLRAP1</i> (1p36.11)	605747/ 603813	Hypercholesterolemia, familial, autosomal recessive
Dynamin 2	<i>DNM2</i> (19p13.2 )	602378/ 606482/ 160150/ 615368	Charcot-Marie-Tooth disease, axonal, autosomal dominant type 2M and dominant intermediate B  Also centronuclear myopathy 1, autosomal dominant, and lethal congenital contracture syndrome 5, autosomal recessive

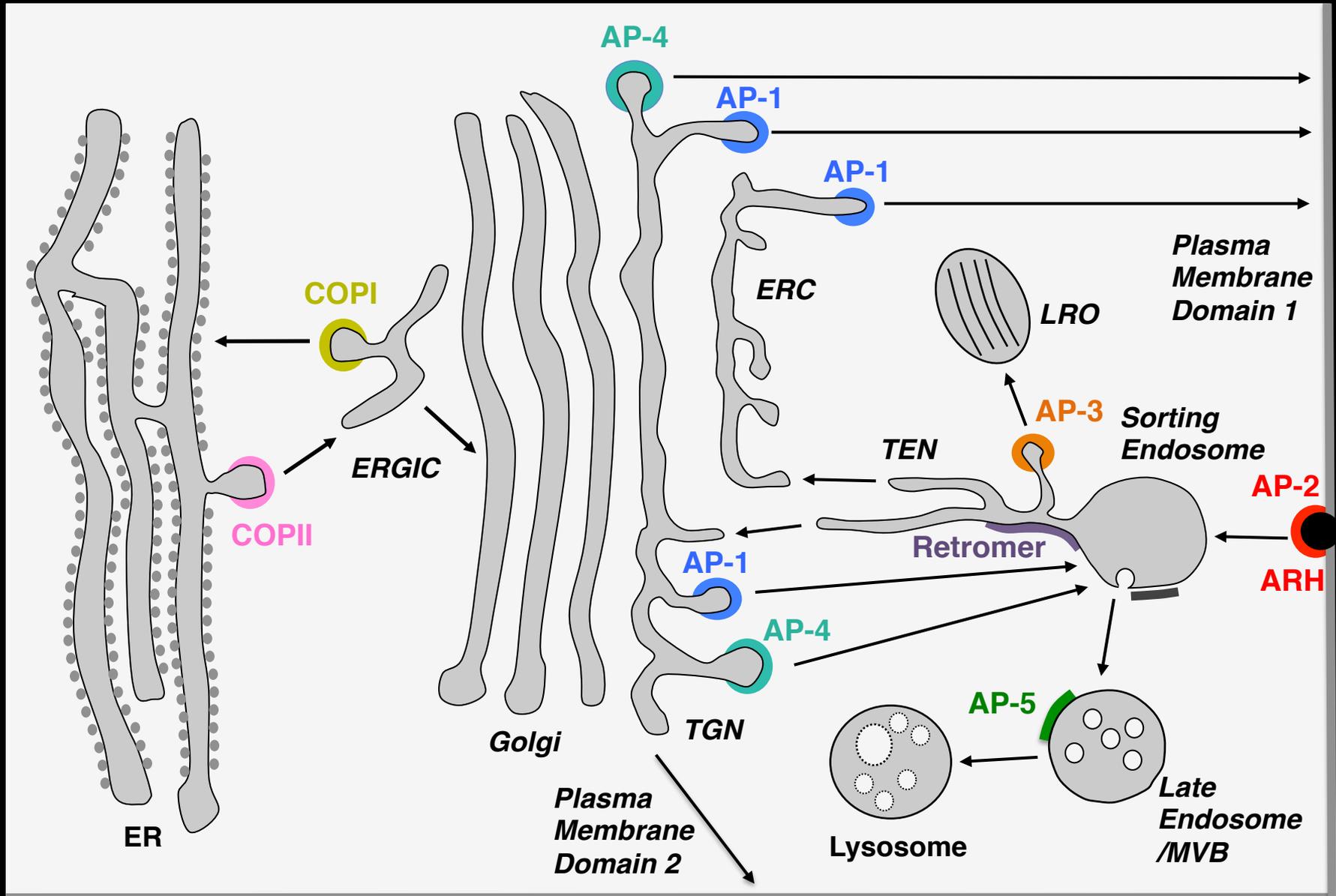
# Protein Coats in the Endomembrane System



# ***Diseases of AP-3 and Related Machinery***

Subunit	Gene	OMIM #	Disease
$\beta$ 3A	<i>AP3B1</i> (5q14.1)	603401/ 608233	Hermansky-Pudlak syndrome 2 (HPS-2)
HPS1	<i>HPS1</i> (10q24.2)	604982/ 203300	Hermansky-Pudlak syndrome 1 (HPS-1)
HPS3	<i>HPS3</i> (3q24)	606118/ 614072	Hermansky-Pudlak syndrome 3 (HPS-3)
HPS4	<i>HPS4</i> (22q12.1)	606682/ 614073	Hermansky-Pudlak syndrome 4 (HPS-4)
HPS5	<i>HPS5</i> (11p15.1)	607521/ 614074	Hermansky-Pudlak syndrome 5 (HPS-5)
HPS6	<i>HPS6</i> (10q24.32)	607522/ 614075	Hermansky-Pudlak syndrome 6 (HPS-6)
HPS7	<i>HPS7</i> (6p22.3)	607145/ 614076	Hermansky-Pudlak syndrome 7 (HPS-7)
HPS8	<i>HPS8</i> (19q13.32)	609762/ 614077	Hermansky-Pudlak syndrome 8 (HPS-8)
HPS9	<i>HPS9</i> (15q21.1)	604310/ 614171	Hermansky-Pudlak syndrome 9 (HPS-9)

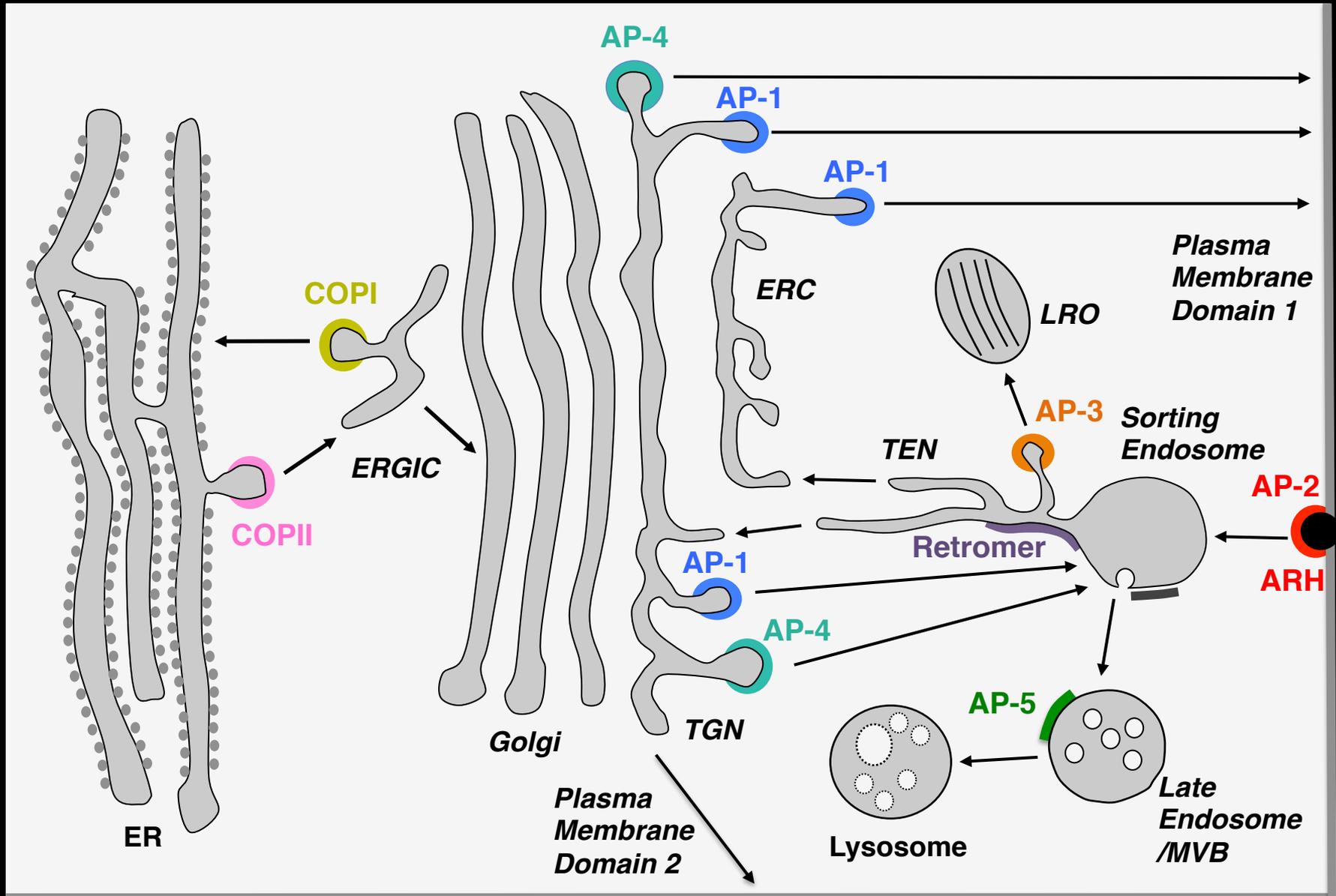
# Protein Coats in the Endomembrane System



# AP-4 Diseases

Subunit	Gene	OMIM #	Disease
$\sigma 4$	<i>AP4S1</i> (14q12)	607243/ 614067	Hereditary spastic paraplegia 52 (SPG52), with thin corpus callosum and mental retardation, autosomal recessive
$\epsilon$	<i>AP4E1</i> (15q21.2)	607244/ 613744	Hereditary spastic paraplegia 51 (SPG51), with thin corpus callosum and mental retardation, autosomal recessive
$\beta 4$	<i>AP4B1</i> (1p13.2)	607245/ 614066	Hereditary spastic paraplegia 47 (SPG47), with thin corpus callosum and mental retardation, autosomal recessive
$\mu 4$	<i>AP4M1</i> (7q22.1)	602296/ 612936	Hereditary spastic paraplegia 50 (SPG50), with thin corpus callosum and mental retardation, autosomal recessive

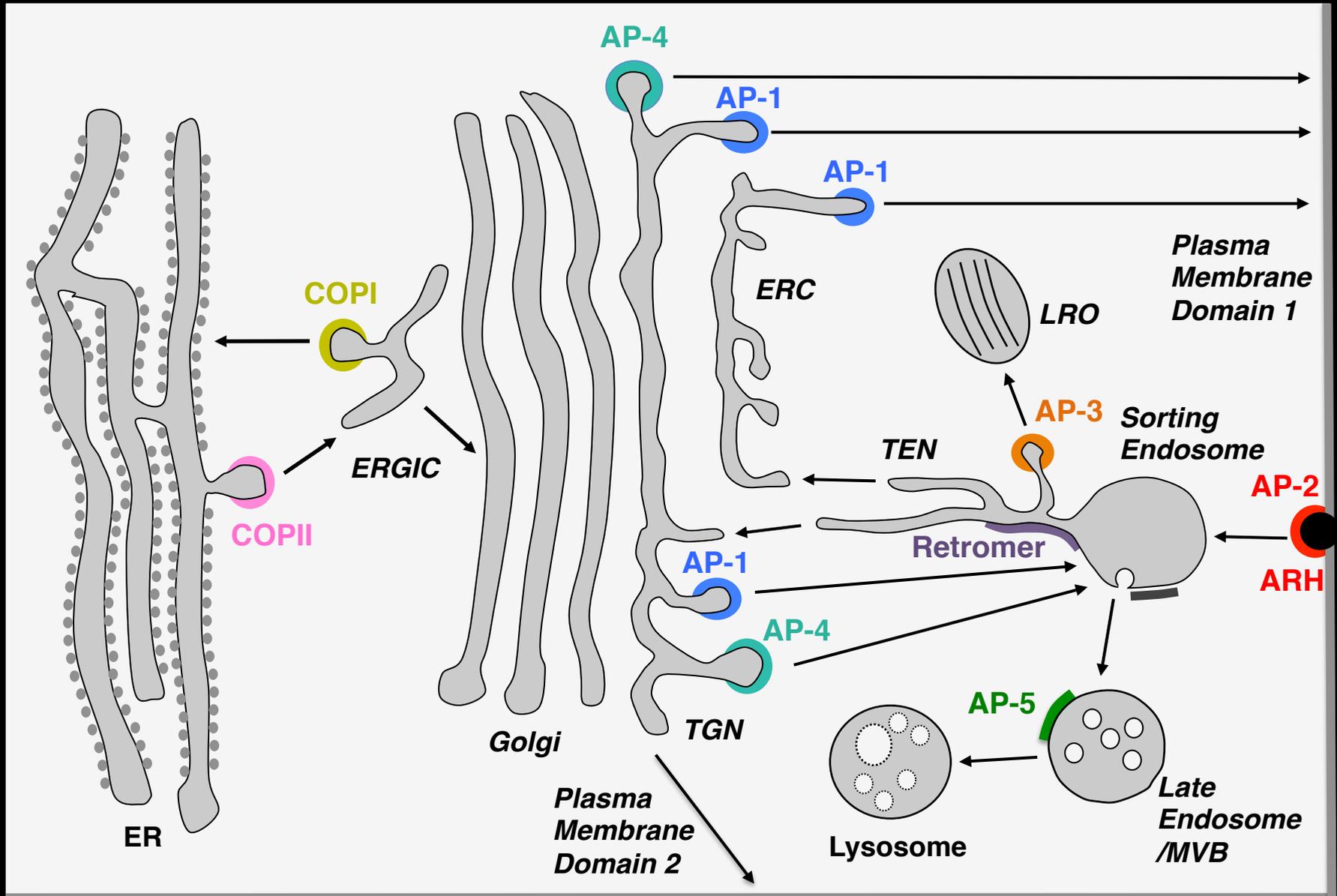
# Protein Coats in the Endomembrane System



# *Diseases of AP-5 and Related Machinery*

Subunit	Gene	OMIM #	Disease
$\xi$	<i>AP5Z1</i> (7p22.1)	613653/ 613647	Hereditary spastic paraplegia 48 (SPG48), with thin corpus callosum and mental retardation, autosomal recessive
Spatacsin	<i>SPG11</i> (15q21.1)	610844/ 604360	Hereditary spastic paraplegia 11 (SPG11), with thin corpus callosum and mental retardation, autosomal recessive
Spastizin	<i>SPG15</i> (14q24.1)	612012/ 270700	Hereditary spastic paraplegia 15 (SPG15), with thin corpus callosum and mental retardation, autosomal recessive

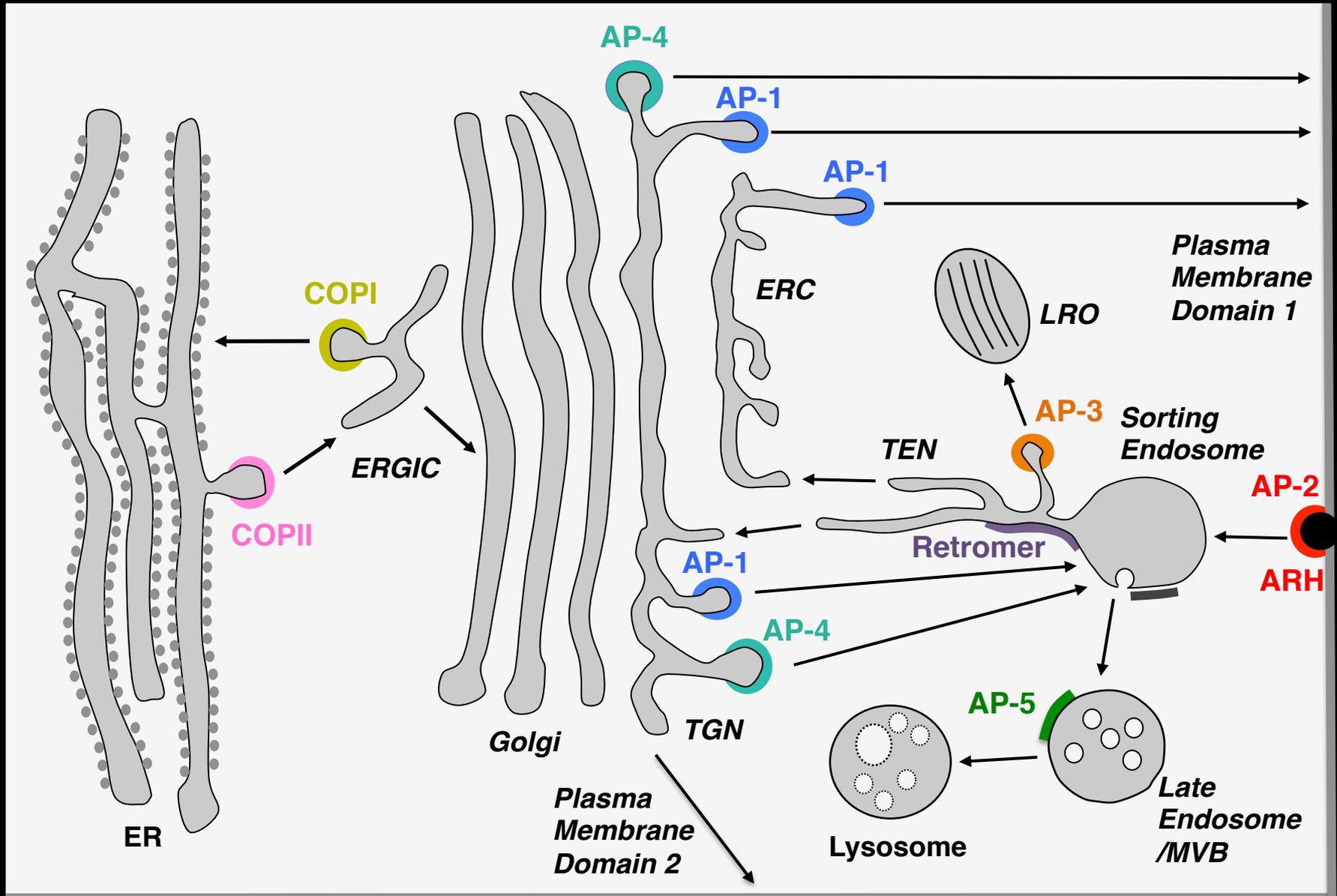
# Protein Coats in the Endomembrane System



# *Diseases of Retromer and Related Machinery*

Subunit	Gene	OMIM #	Disease
Vps35	<i>VPS35</i> (16q11.2)	614203/ 601501	Parkinson disease 17, autosomal dominant, adult-onset
Rme8 (DNAJC13 )	<i>DNAJC13</i> (3q22.1)	614334	Parkinson disease, autosomal dominant, adult-onset
Rab7L1	<i>RAB7L1</i> (1q32.1)	603949/ 613164	Parkinson disease 16
Lrrk2	<i>LRRK2</i> (12q12)	609007/ 607060	Parkinson disease 8, autosomal dominant, adult-onset

# Protein Coats in the Endomembrane System



# *Genetic Disorders of Protein Coats*

---

- Protein coats involved in intracellular transport
- Diseases caused by mutations in coat proteins
- **AP-3 defects in Hermansky-Pudlak Syndrome**
- AP-1 defects in neurodevelopmental disorders

# ***AP-3 Defects in the Hermansky-Pudlak Syndrome (HPS)***

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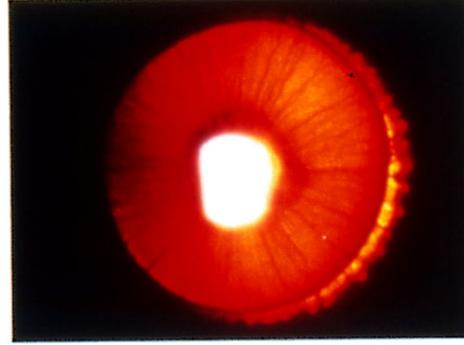
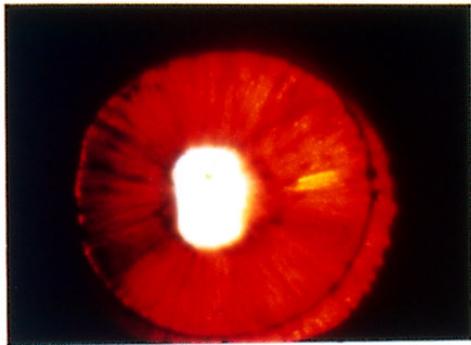
- **Autosomal recessive disorder**

# ***AP-3 Defects in the Hermansky-Pudlak Syndrome (HPS)***

---

- **Autosomal recessive disorder**
- **Oculocutaneous albinism**

# *Oculocutaneous Albinism in HPS*



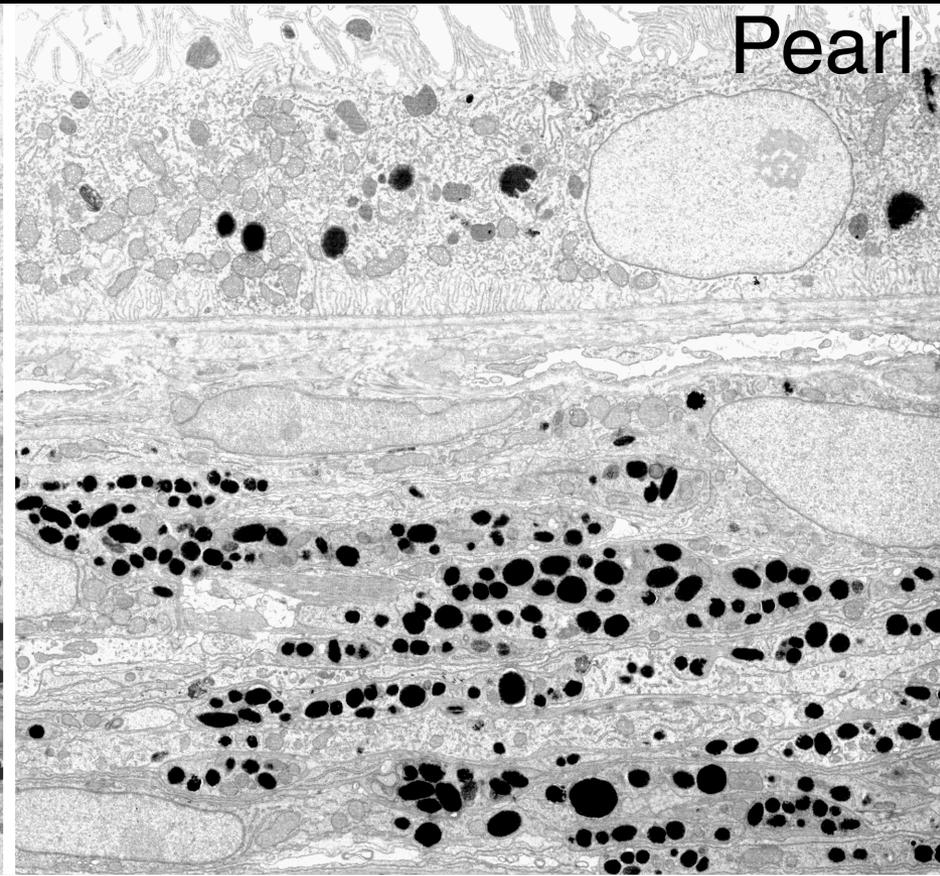
# ***AP-3 Defects in the Hermansky-Pudlak Syndrome (HPS)***

---

- **Autosomal recessive disorder**
- **Oculocutaneous albinism**

***Abnormal melanosomes***

# ***Abnormal Melanosomes in HPS***



# ***AP-3 Defects in the Hermansky-Pudlak Syndrome (HPS)***

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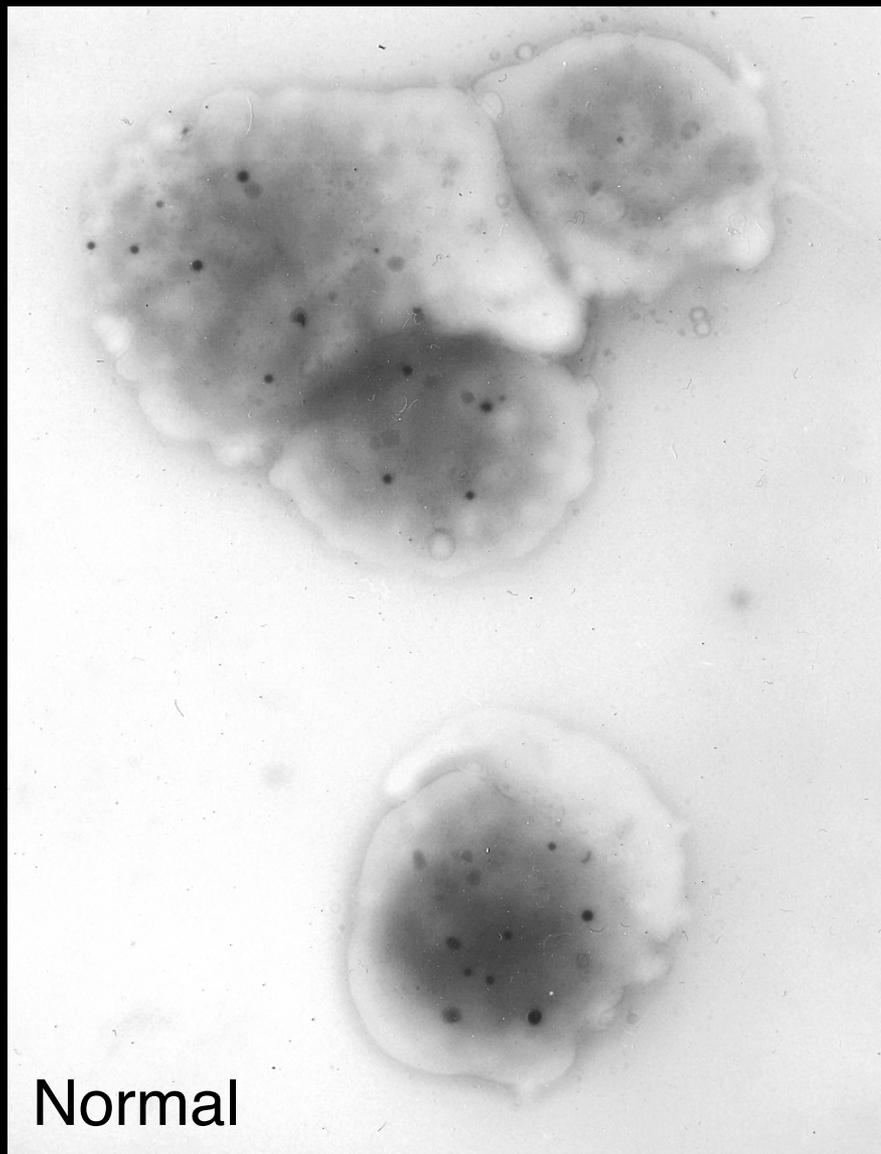
- **Autosomal recessive disorder**
- **Oculocutaneous albinism**

***Abnormal melanosomes***

- **Prolonged bleeding**

***Absence of platelet dense granules***

# ***Absence of Platelet Dense Granules in HPS***



# ***AP-3 Defects in the Hermansky-Pudlak Syndrome (HPS)***

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***Absence of platelet dense granules***

- **Fibrosis of the lungs, inflammatory colitis**

***Accumulation of ceroid lipofuscin in cells of the reticuloendothelial system***

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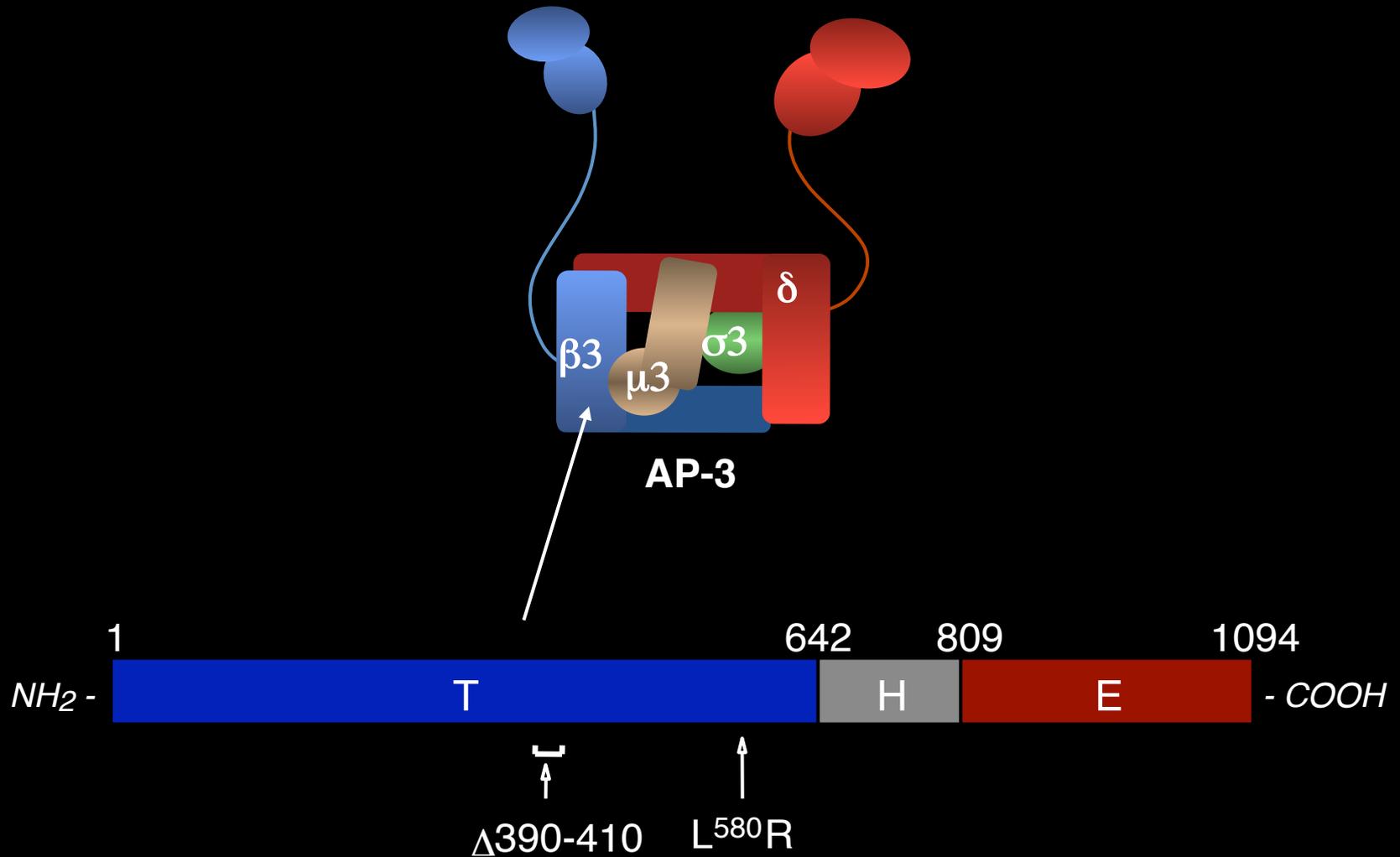
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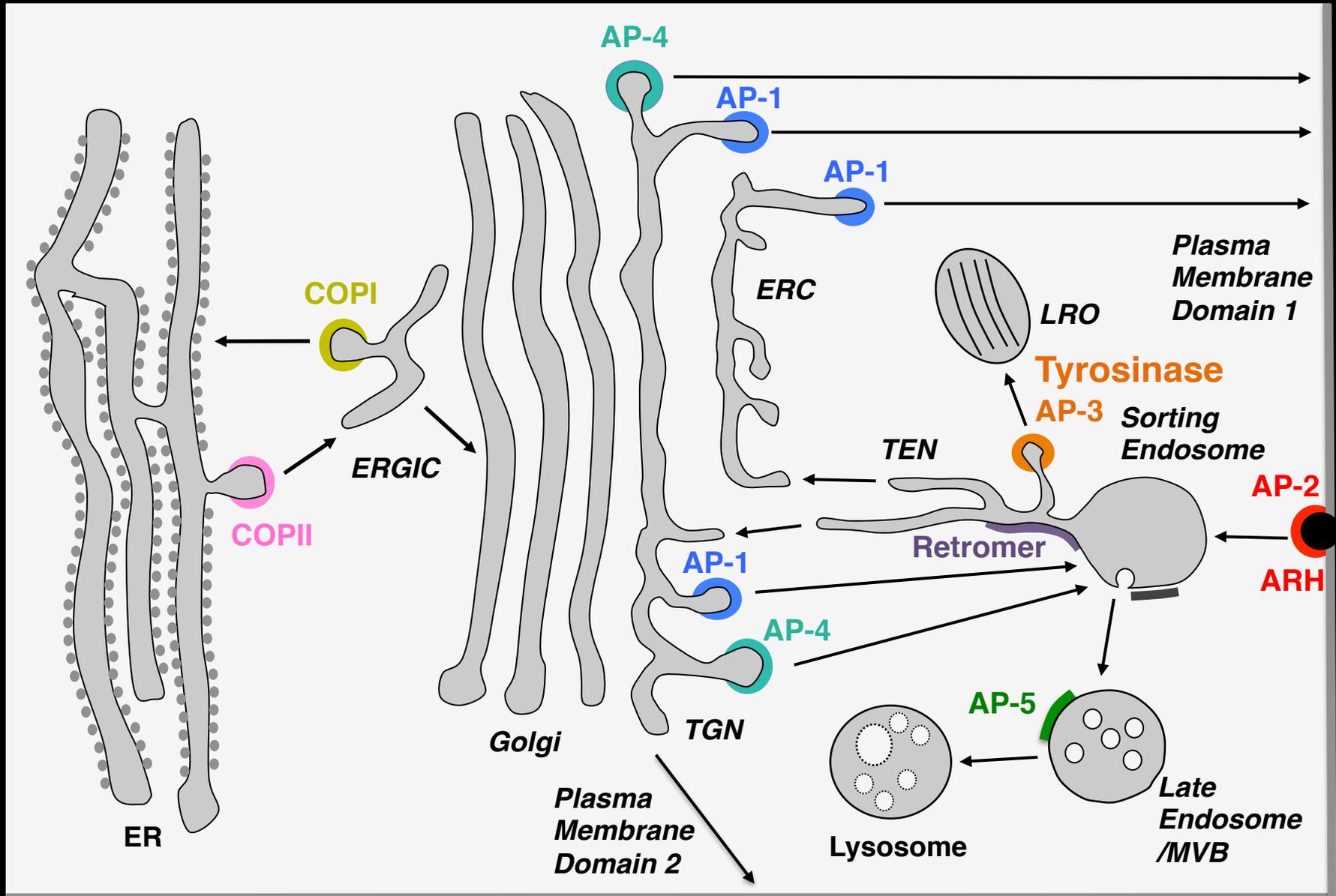
***Accumulation of ceroid lipofuscin in cells of the reticuloendothelial system***

- **Others: facial dysmorphism, neutropenia, impaired CTL and NK responses, frequent infections**

# Mutations in $\beta 3A$ in HPS-2



# Protein Coats in the Endomembrane System



# HPS Patients

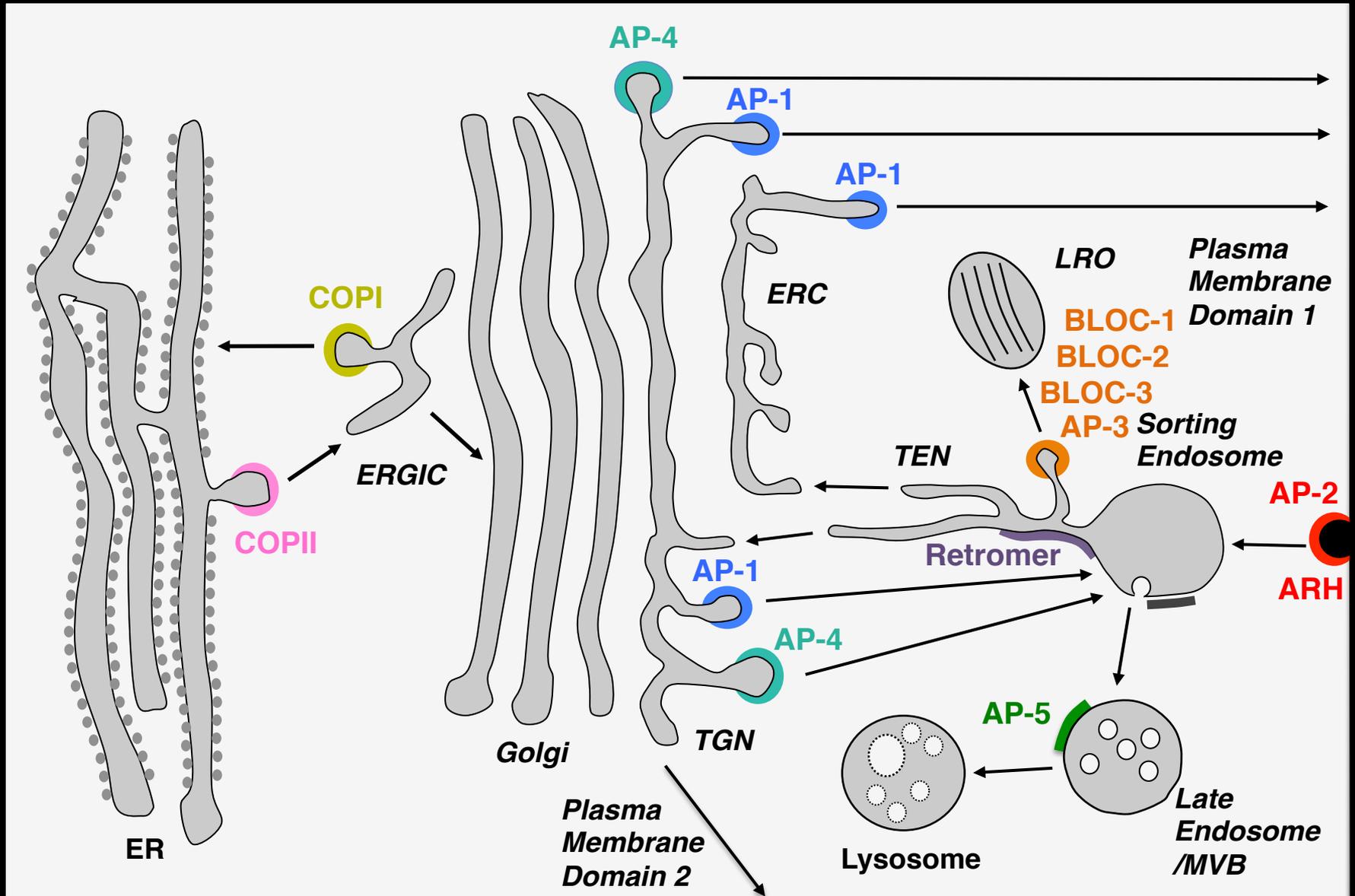


Photos courtesy of William Gahl

# ***Diseases of AP-3 and Related Machinery***

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HPS1	HPS1 (10q24.2)	604982/ 203300	Hermansky-Pudlak syndrome 1 (HPS-1)
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HPS9	HPS9 (15q21.1)	604310/ 614171	Hermansky-Pudlak syndrome 9 (HPS-9)

# BLOC Defects in HPS



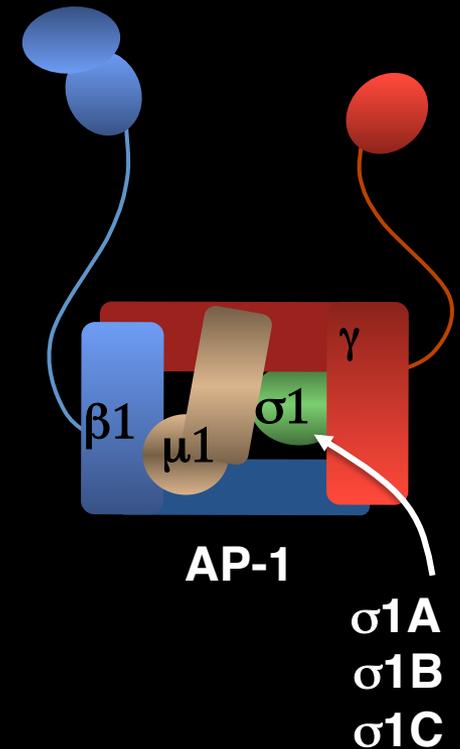
# *Genetic Disorders of Protein Coats*

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- Protein coats involved in intracellular transport
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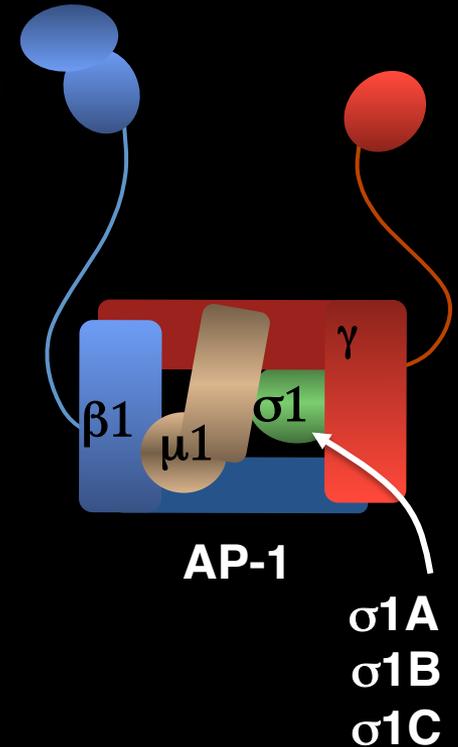
# MEDNIK Syndrome ( $\sigma 1A$ mutation)

- Autosomal recessive
- **M**ental retardation
- **E**nteropathy
- **D**eafness
- **N**europathy
- **I**chthyosis
- **K**eratodermia

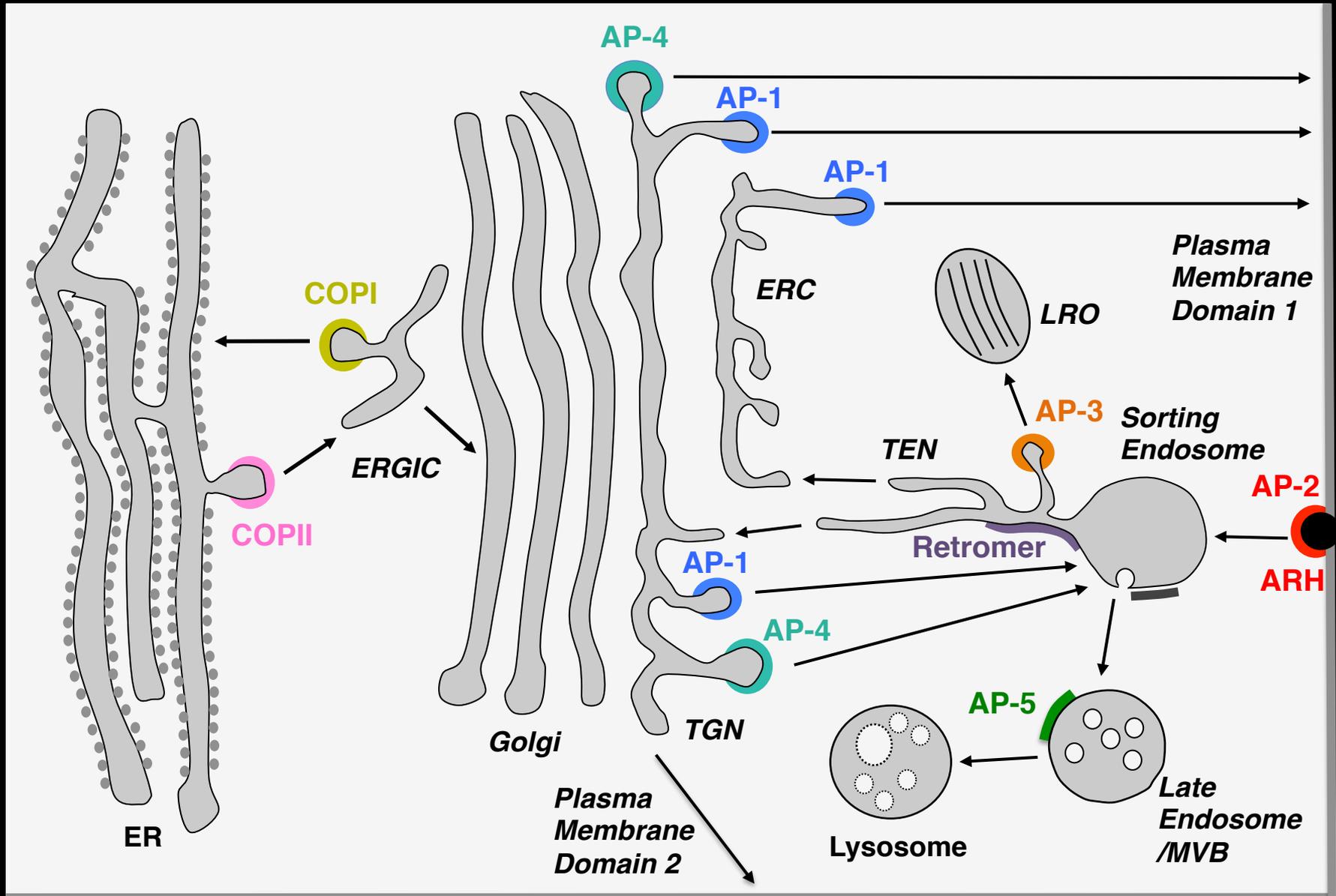


# ***Fried Syndrome/Pettigrew Syndrome ( $\sigma 1B$ mutation)***

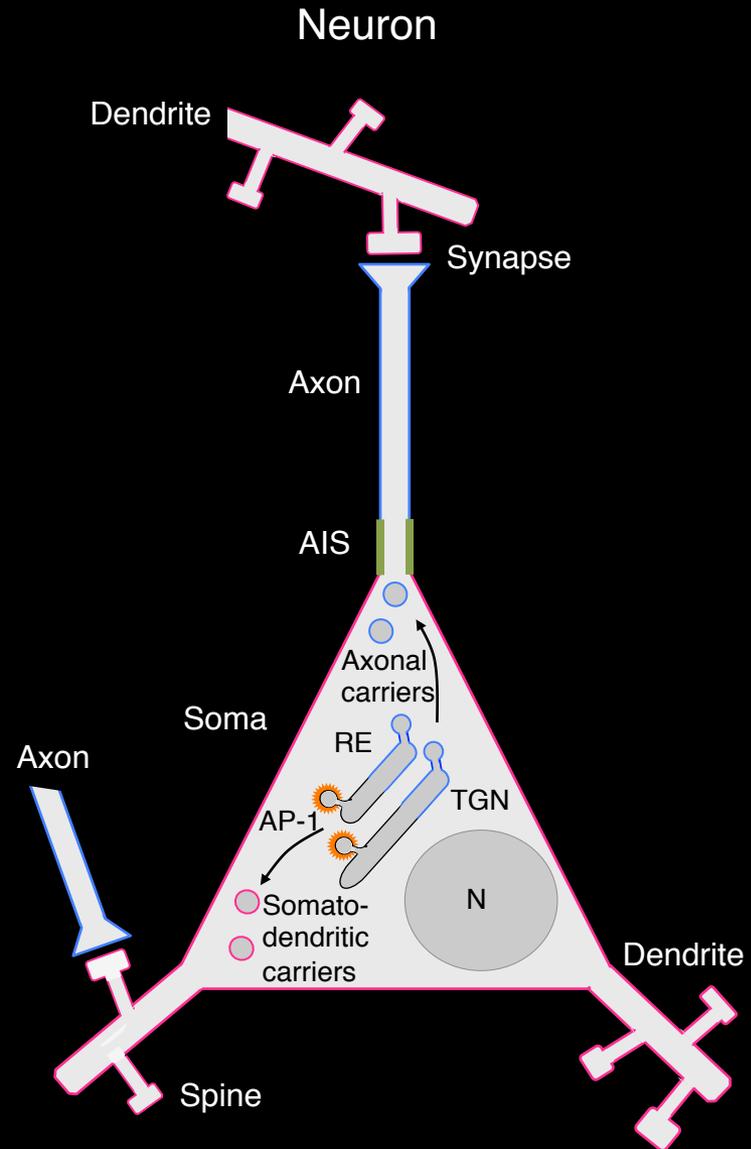
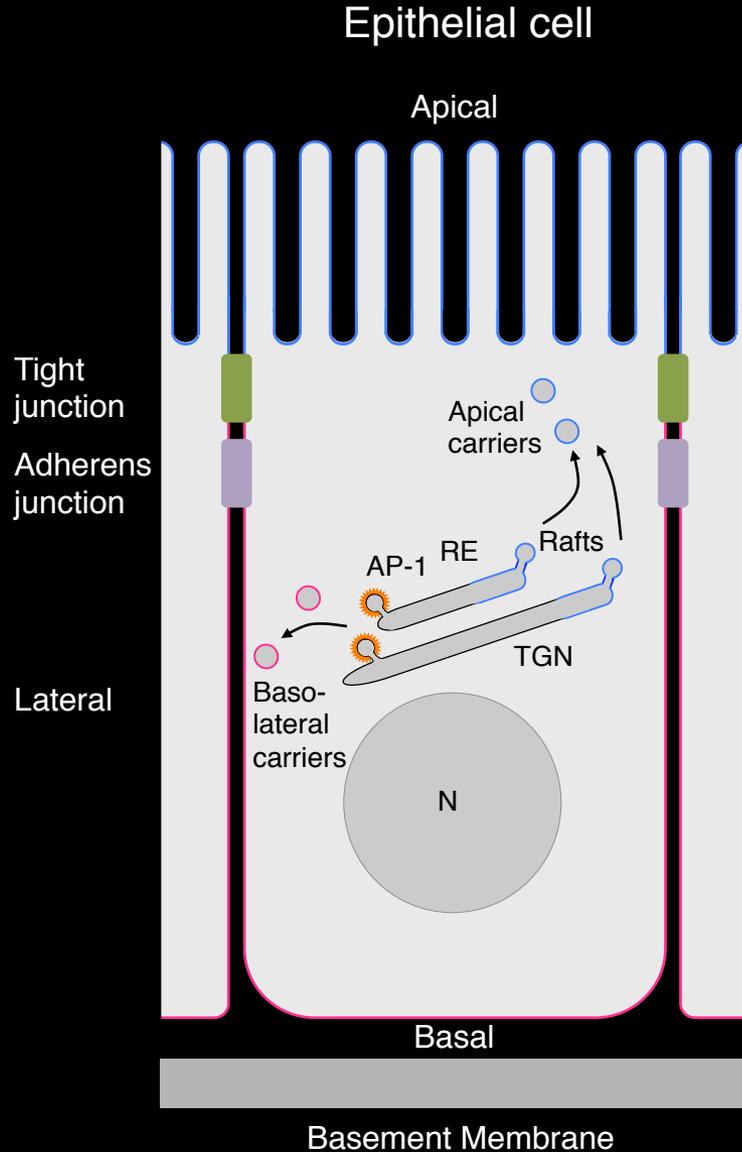
- **X-linked mental retardation**
- **Dandy-Walker malformation of the cerebellum**
- **Hydrocephalus; stenosis of the aqueduct of Sylvius**
- **Ventral ganglia calcification and iron deposition**
- **Cerebral palsy**
- **Delayed motor development**
- **Hypotonia**
- **Aggressive behavior**
- **Facial dysmorphism**



# Protein Coats in the Endomembrane System



# AP-1 Mediates Polarized Sorting in Epithelial Cells and Neurons



# *MEDNIK Syndrome ( $\sigma$ 1A mutation)*

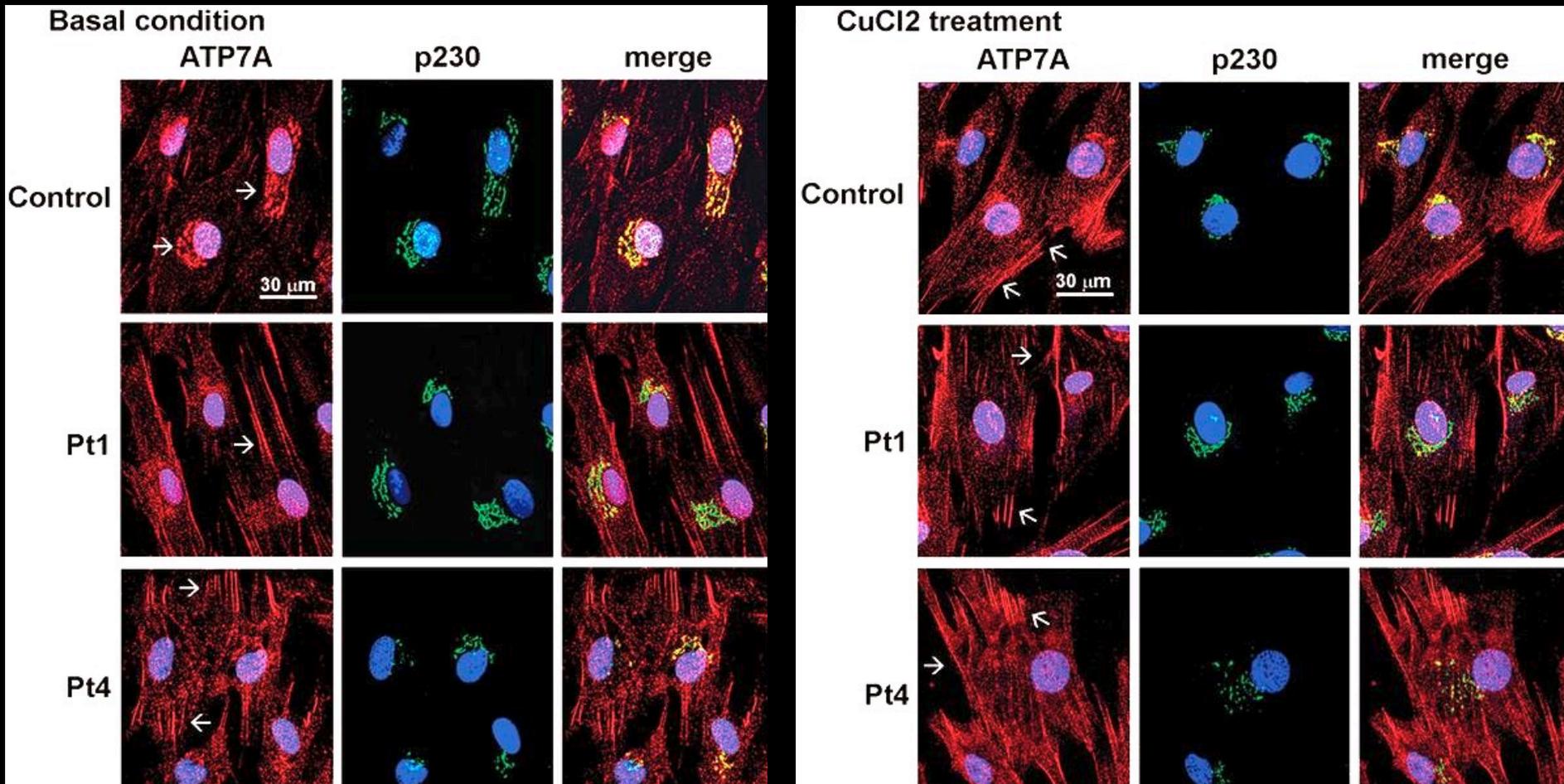
## **MEDNIK syndrome: a novel defect of copper metabolism treatable by zinc acetate therapy**

Diego Martinelli,<sup>1,\*</sup> Lorena Travaglini,<sup>2,\*</sup> Christian A. Drouin,<sup>3</sup> Irene Ceballos-Picot,<sup>4</sup> Teresa Rizza,<sup>2</sup> Enrico Bertini,<sup>2</sup> Rosalba Carrozzo,<sup>2</sup> Stefania Petrini,<sup>5</sup> Pascale de Lonlay,<sup>6</sup> Maya El Hachem,<sup>7</sup> Laurence Hubert,<sup>6</sup> Alexandre Montpetit,<sup>8</sup> Giuliano Torre<sup>9</sup> and Carlo Dionisi-Vici<sup>1</sup>

### **In addition to neurocutaneous phenotype:**

- **Hypocupremia, hypoceruloplasminemia**
- **Liver copper accumulation**
- **Hepatomegaly, increased transaminases, cholestasis**
- **Decreased cuproenzymes: COX II and IV, SOD**
- **Characteristics of both Menkes and Wilson diseases**

# Abnormal Traffic of ATP7A in MEDNIK Patients



# *Zinc Acetate Improves MEDNIK Symptoms*

---

- **Zinc acetate or sulfate is used to treat Wilson's disease.**
- **Zinc induces intestinal cell metallothionein, blocking copper absorption from the intestinal tract.**
- **Treatment of a MEDNIK patient with zinc acetate normalized plasma copper, ceruloplasmin, transaminases and bile acid levels, and reduced liver copper overload.**
- **Importantly, zinc acetate treatment improved behavioral disturbances, cognitive function and itching**